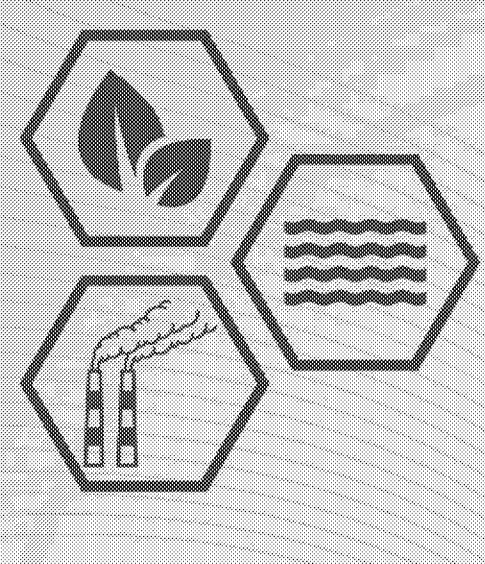
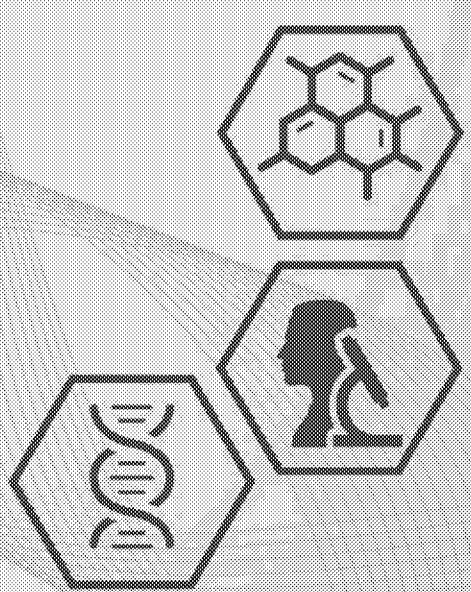


Toxicological Profile for Glyphosate

Draft for Public Comment

May 2017



ATSDR
U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch

Regular Mailing Address:
1600 Clifton Road, N.E.
Mail Stop F-57
Atlanta, Georgia 30329-4027

Physical Mailing Address:
4770 Buford Highway
Building 102, 1st floor, MS F-57
Chamblee, Georgia 30341

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

VERSION HISTORY

Date	Description
DATE PENDING	Draft for public comment toxicological profile released

CONTRIBUTORS & REVIEWERS

Hana Pohl, M.D., Ph.D. (Lead)
Selene Chou, Ph.D.
Mike Fay, Ph.D.
Carolyn Harper, Ph.D.
Melanie Buser, M.P.H.
Susan Zells Ingber, A.B., M.S.P.P.

ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

David W Wohlers, Ph.D.
Mario Citra, Ph.D.
Christina Coley, B.S.
Lisa Ingerman, Ph.D., DABT

SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:
Includes ATSDR; National Center for Environmental Health (NCEH); National Institute of Occupational Health and Safety (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:
ATSDR, Division of Community Health Investigations; NCEH, Division of Laboratory Science; U.S. Department of Defense.

PEER REVIEWERS

1.
2.
3.

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Glyphosate is a phosphonoglycine non-selective herbicide, first registered for use by the EPA in 1974. Glyphosate is typically manufactured for commercial use as a salt available in soluble liquid and soluble granule formulations. Herbicide formulations employing glyphosate salts are commonly produced in combination with additives, inert ingredients, and surfactants. The salt derivatives enhance absorption of glyphosate from the surface of the plant or leaf structure, but are not the herbicidally active portion of the compound. Specific formulations vary in composition and are marketed under numerous trade names (PAN 2009). Commercial products containing glyphosate may have concentrations ranging from 0.96 to 94 w/w%. For example, the common herbicide, Roundup, has product formulations containing glyphosate concentrations ranging from 0.96 to 62.0 w/w% (IPCS 1994).

The manufacture and use of glyphosate as a broad spectrum contact herbicide applied to a wide variety of fruits, vegetables, grains, and agricultural crops has led to its direct release into the environment (EPA 1993). Glyphosate is produced commercially in the United States as a technical-grade substance with a purity of ≥95% (McBean 2011). In 2007, U.S. agricultural use of glyphosate was approximately 82,800 tons and non-agricultural use of glyphosate was 9,300 tons (Battaglin et al. 2014). Once glyphosate enters the environment, it has low potential for environmental persistence and is unlikely to bioaccumulate; the chemical is either degraded by microbial processes or inactivated by adsorption to soil (Smith and Oehme 1992). Glyphosate is expected to adsorb to soils under most environmental conditions; therefore, leaching into groundwater is minimal. Glyphosate may enter surface waters due to its limited use in some aquatic environments. Volatilization of glyphosate is not an important fate process based on its low vapor pressure and ionic nature. Transport in the air after spray applications is dependent on meteorological conditions; ground and aerial applications can result in spray drift, which may affect non-target plants (PAN 2009; Yates et al.1978).

The general population may be exposed to glyphosate by dermal contact with consumer products, crops, foliage, or soils containing residues of this chemical; ingestion of plants, crops, foods, or waters containing residues of this chemical; and inhalation of mist or spray during the use of products containing this chemical. The greatest potential for exposure can be expected for populations residing near agricultural areas and crop farms, manufacturing and processing plants where glyphosate is produced or used, and hazardous waste disposal sites containing glyphosate; these populations may be exposed to higher than average environmental concentrations of glyphosate.

Occupational exposure of glyphosate may occur via dermal contact or inhalation during manufacture, transport, and disposal. Occupational exposure may occur via dermal and ocular routes from accidental splashes during mixing operations, loading of products, and application of herbicides containing glyphosate. Farmers and home gardeners using herbicides containing glyphosate may be exposed to glyphosate via dermal contact and inhalation. Dermal contact appears to be the major route of exposure to glyphosate for workers involved in its application.

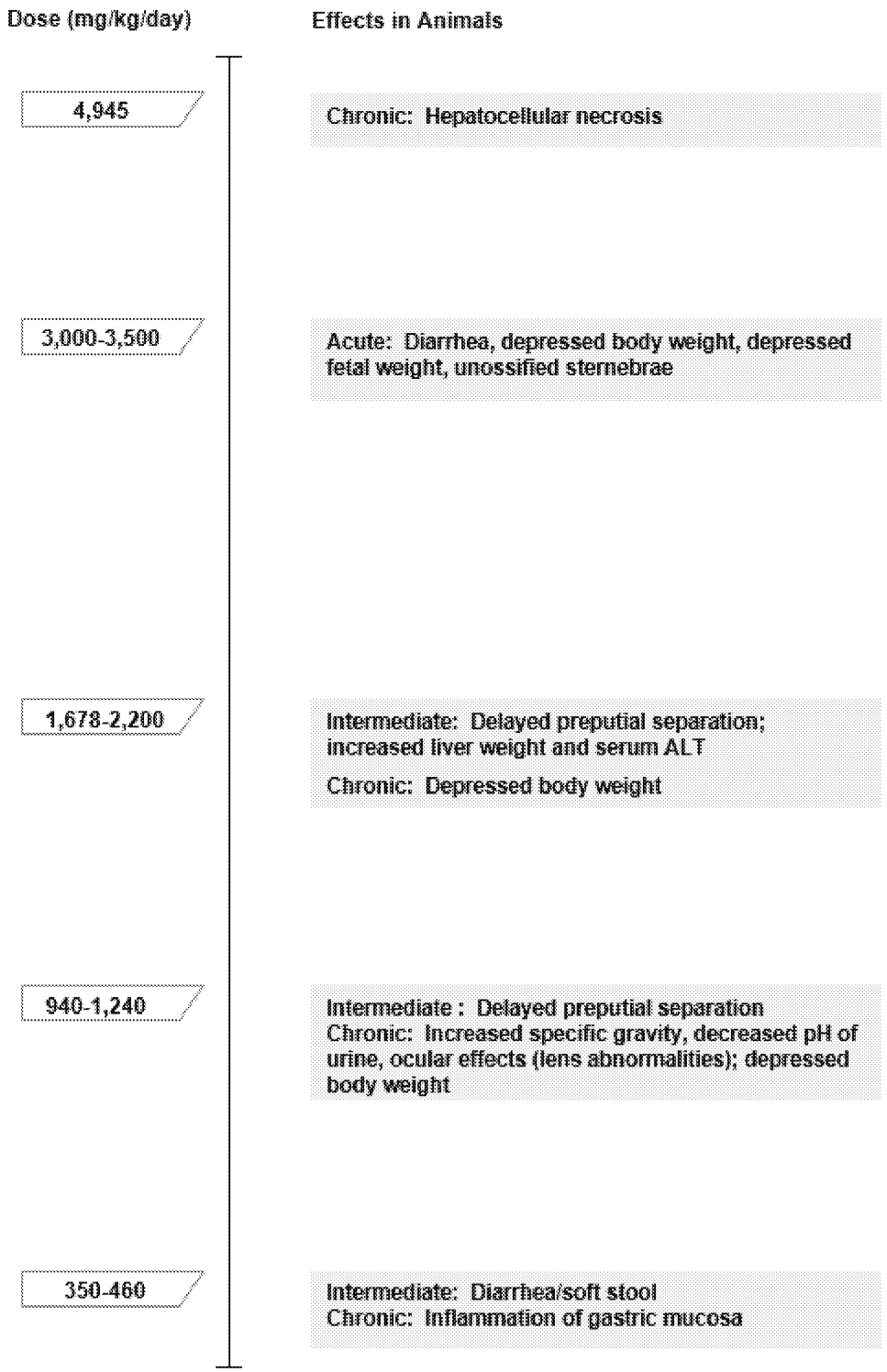
Children are expected to be exposed to glyphosate by the same routes as adults in the general population. Due to increased hand-to-mouth activity and playing habits, children are more likely to come into contact with glyphosate residues that may be present in soil. No data were located regarding glyphosate concentrations in breast milk; therefore, no determination on the importance of this route for child exposure has been made. In one small study, neither glyphosate nor its major degradation product, aminomethylphosphonic acid (AMPA), were detected in the maternal or fetal cord serum of pregnant subjects (Aris and LeBlanc 2011). Although the results of this study indicate that *in utero* exposure to glyphosate may not be of particular concern to human health, additional data are needed for more fully assess the potential hazard of *in utero* exposure to glyphosate.

See Chapter 5 for more detailed information regarding concentrations of glyphosate in environmental media.

1.2 SUMMARY OF HEALTH EFFECTS

Information regarding the toxicity of glyphosate comes primarily from oral studies in laboratory animals exposed to glyphosate technical. No information was located regarding health effects in humans exposed to glyphosate technical; human exposures are to herbicides that contain glyphosate and other ingredients. A few animal studies evaluated the effects of oral dosing with glyphosate formulations containing surfactant and additional unspecified substances. Reported effects may be due, at least in part, to the surfactant. Therefore, Figure 1-1 contains summary information related only to glyphosate technical. As illustrated in Figure 1-1, gastrointestinal disturbance appears to be the most sensitive noncancer effect of glyphosate technical toxicity. Ocular, hepatic, renal, and body weight effects were observed at repeated-oral doses ≥940 mg/kg/day. Developmental effects were observed at dose levels resulting in maternal toxicity as well.

Figure 1-1. Noncancer Health Effects Found in Animals Following Oral Exposure to Glyphosate Technical



Gastrointestinal Effects. Gastrointestinal symptoms are commonly reported in case reports of patients ingesting glyphosate products. Soft stool and/or diarrhea were reported in pregnant rabbits gavaged with glyphosate technical during gestation days (GDs) 6–27 (EPA 1992f) and rats administered glyphosate technical in the diet for 2 generations (EPA 1992a). Inflammation of gastric mucosa was observed in female rats orally exposed to glyphosate technical for 2 years (EPA 1991a, 1991b).

Body Weight Effects. Depressed body weight was observed during intermediate- and chronic-duration oral exposure of laboratory animals to glyphosate technical at doses ≥1,183 mg/kg/day (EPA 1985a, 1991a, 1991b, 1992a).

Hepatic Effects. Increased liver weight and increased serum markers of liver effects (alkaline phosphatase [AP], alanine aminotransferase [ALT], and/or bile acids) were observed in rats administered glyphosate technical for 13 weeks at ≥1,678 mg/kg/day (NTP 1992). Centrilobular hepatocellular necrosis was observed in livers from male mice administered glyphosate technical for 2 years at an estimated dose of 4,945 mg/kg/day (EPA 1985a).

Renal Effects. Increased specific gravity of urine and decreased urinary pH were noted among male rats administered glyphosate technical for 2 years at 940 mg/kg/day (EPA 1991a, 1991b). Female mice administered glyphosate technical for 2 years at 6,069 mg/kg/day exhibited significantly increased incidence of renal proximal tubule epithelial basophilia and hypertrophy (EPA 1985a).

Ocular Effects. In a report of human case series of 1,513 ocular exposures to glyphosate, minor symptoms (primarily transient irritation) were observed in 70% of the cases; most (99%) complained of eye pain (Acquavella et al. 1999). Lens abnormalities were observed in male rats administered glyphosate technical for 2 years at 940 mg/kg/day (EPA 1991a, 1991b).

Developmental Effects. Several epidemiology studies reported associations between maternal preconception exposure to glyphosate and increased risk of spontaneous abortion (Arbuckle et al. 2001) and glyphosate exposure and parent-reported attention deficit disorder/attention deficit hyperactivity disorder (Garry et al. 2002). Depressed weight and increased incidence of unossified sternebrae were observed in GD 20 fetuses from rat dams treated with glyphosate technical by gavage at 3,500 mg/kg/day during GDs 6–19 (EPA 1992e). In a study of rats exposed via the diet for 2 generations, up to 14–20% depressed pup body weight and/or body weight gain at an estimated glyphosate technical dose of

3,134 mg/kg/day (EPA 1992a). In another 2-generation oral rat study, an estimated glyphosate technical dose of 1,234 mg/kg/day resulted in delayed preputial separation (EPA 2013a).

Cancer Effects. The carcinogenic potential of glyphosate has been evaluated in a number of case-control and cohort epidemiology studies. Most of the studies used self-reported ever/never glyphosate use as the biomarker of exposure, and subjects were likely exposed to other pesticides as well. Most studies found no significant associations between glyphosate and various cancer types. A few studies reported a significant association between self-reported glyphosate use and risk of non-Hodgkin's lymphoma; other studies found no significant association. The carcinogenic potential of glyphosate has also been evaluated in a number of unpublished animal studies. The U.S. Environmental Protection Agency (EPA) provided ATSDR with reviews and/or Data Evaluation Records (DERs) for two rat studies (EPA 1991a, 1991b, 1992d) and one mouse study (EPA 1985a, 1985b, 1986b, 1993, 2015a, 2016b). There was no evidence of carcinogenicity in the rat studies. There was no clear evidence of carcinogenicity in the mouse study, although 3 of 50 male mice ingesting glyphosate at an extremely high dose (nearly 5,000 mg/kg/day) exhibited rare kidney tumors compared to only 1 of 49 control males (statistically nonsignificant).

In a recent evaluation of the carcinogenic potential of glyphosate, EPA's Office of Pesticide Programs (EPA 2016a) considered the weight-of-evidence from human and animal data to support a classification of "not likely to be carcinogenic to humans" at doses relevant to human health risk assessment. The International Agency for Research on Cancer (IARC 2015, 2016) has classified glyphosate as Group 2A (*probably carcinogenic to humans*), based on conclusions that there is "*limited evidence*" in humans and "*sufficient evidence*" in animals. The Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Meeting on Pesticide Residues (JMPR), another subdivision of WHO, concluded that glyphosate was unlikely to pose a carcinogenic risk to humans from exposure through the diet (FAO and WHO 2016). The European Food Safety Authority (EFSA) determined that glyphosate was unlikely to pose a carcinogenic hazard to humans (EFSA 2015). The U.S. Department of Health and Human Services Report on Carcinogens (14th edition) does not include an evaluation of glyphosate (NTP 2016).

1.3 MINIMAL RISK LEVELS (MRLs)

A minimal risk level (MRL) is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given

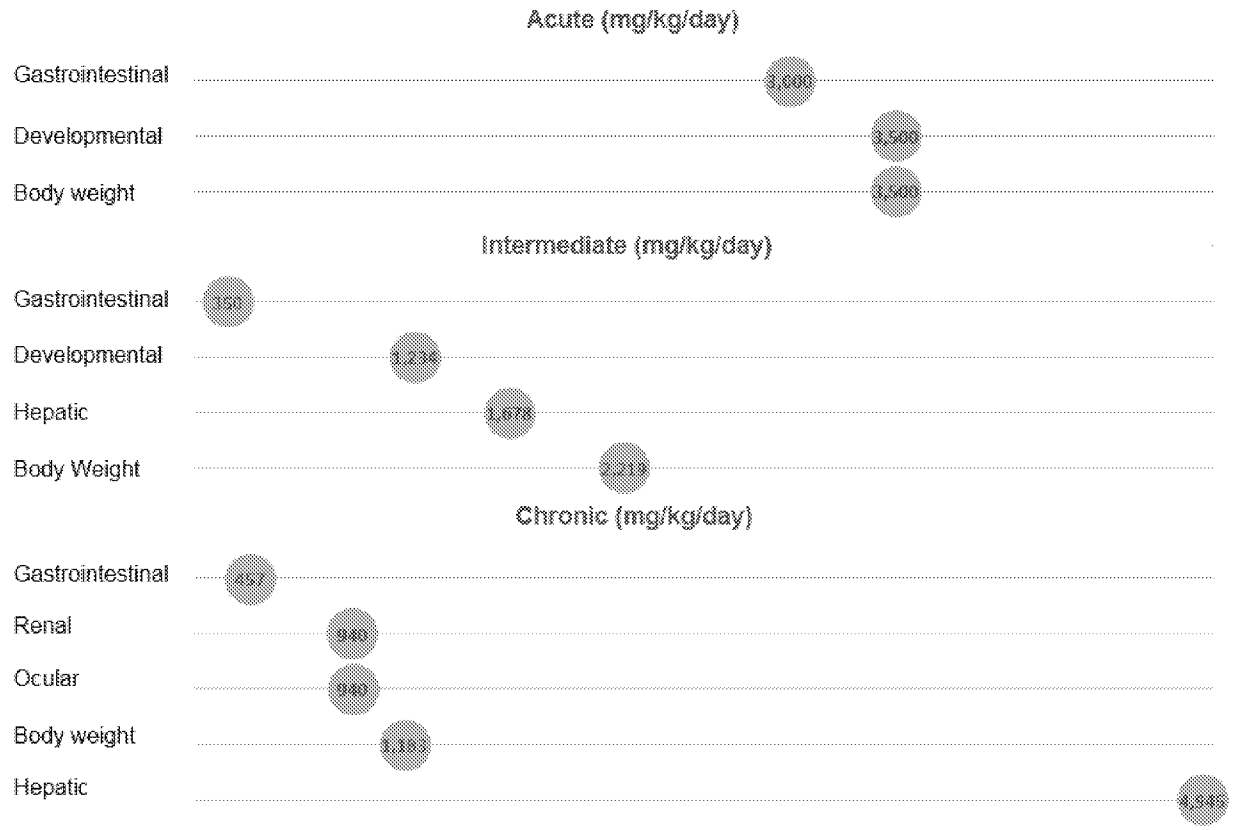
route of exposure. MRLs are based on noncancerous health effects only; carcinogenic effects are not considered. MRLs can be derived for acute-, intermediate-, and chronic-duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Animal studies submitted to EPA's Office of Pesticides Programs to fulfill requirements for the registration of a particular glyphosate formulation for use in the U.S. involve exposure to glyphosate technical (typically < 90% purity). Some animal studies in the open literature used glyphosate formulations that typically included 1-41% glyphosate technical (or glyphosate salts) and up to 18% surfactant (along with other "inert" ingredients). Surfactants in glyphosate formulations are at least partly responsible for the toxic effects from overexposure to glyphosate formulations (Adam et al. 1997; Sawada et al. 1988; Williams et al. 2000). The general population will not be exposed to glyphosate technical, but rather to glyphosate formulations registered for use. MRLs based on animal exposure to glyphosate technical would not adequately reflect human exposure to glyphosate formulations. Therefore, no MRLs were derived for glyphosate technical. No MRLs were derived for glyphosate formulations due to the wide variation in glyphosate content and surfactants used in various glyphosate formulations and the fact that surfactants contribute to the toxicity of glyphosate formulations.

As illustrated in Figure 1-2, gastrointestinal disturbance appears to be the most sensitive effect of glyphosate technical toxicity.

Figure 1-2. Summary of Sensitive Targets of Glyphosate Technical – Oral

The gastrointestinal tract is the most sensitive target of ingested glyphosate technical. Numbers in circles are the lowest LOAELs (mg/kg/day) for all health effects in animals; no reliable dose-response data were available for humans.



CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of glyphosate. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to glyphosate, but may not be inclusive of the entire body of literature.

Animal oral study information for glyphosate technical is presented in Table 2-1 and Figure 2-3. Animal oral study information for glyphosate formulations is presented in Table 2-2 and Figure 2-4. Animal dermal study information for glyphosate technical is presented in Table 2-3.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. LSE tables and figures for animal inhalation studies of glyphosate technical and glyphosate formulations are precluded by lack of publicly-available data. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or

death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

Roundup (containing glyphosate as the active ingredient) is the most widely used herbicide worldwide in both agricultural and residential applications. Glyphosate technical (purity typically >95%) has been evaluated in numerous animal studies, most of which employed the oral exposure route and were submitted to EPA's Office of Pesticide Programs through the pesticide registration program as directed by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Federal Food, Drug and Cosmetic Act (FFDCA), and Food Quality Protection Act (FQPA). The submitted studies are generally unpublished proprietary studies not available to the public. EPA evaluated submitted study reports and produced summaries termed Data Evaluation Records or Data Evaluation Reports (DERs) that include EPA's own conclusions regarding study design, results, and conclusions of the study authors. Information from DERs received from EPA and cleared for release to the public is summarized in this ATSDR Toxicological Profile for Glyphosate. Results from unpublished studies and/or EPA summaries that have not presently been cleared for release to the public are not summarized in this Toxicological Profile. Some unpublished or proprietary animal studies of glyphosate were submitted by various chemical companies to agencies or organizations outside the United States for product registration purposes. EPA's Office of Pesticide Programs evaluated some of these unpublished or proprietary studies and released "Abbreviated Data Evaluation Records" that included limited study details (e.g., EPA 2016b). ATSDR elected not to include the abbreviated DER information in this Toxicological Profile because the unpublished studies were not available to ATSDR for independent review and EPA's abbreviated DERs were considered too limited in study details.

This ATSDR Toxicological Profile for Glyphosate includes publicly-available data for glyphosate technical (purity typically >95%) and glyphosate formulations (typically 1–41% glyphosate technical or glyphosate salts and ≤18% polyoxyethyleneamine surfactant). Surfactants in glyphosate formulations are at least partly responsible for the toxic effects from overexposure to glyphosate formulations (Adam et al. 1997; Sawada et al. 1988; Williams et al. 2000).

Epidemiological studies of glyphosate are predominantly case-control and cohort epidemiology studies that examined possible associations between exposure to glyphosate (in glyphosate-containing herbicides) and selected health outcomes (noncancer and cancer endpoints), or case reports following accidental or intentional ingestion of glyphosate-containing products. These epidemiology studies are summarized in Table 2-4 (noncancer) and Table 2-5 (cancer). The majority of the studies used self-reported (or proxy reported) ever/never glyphosate use as the biomarker of exposure and some studies included a metric for frequency of exposure. There is no information regarding health effects in humans exposed to glyphosate technical.

Most reliable health effects data come from oral studies of animals administered glyphosate technical (see Figure 2-1 for an overview of the number of animal studies examining potential endpoints of concern from oral exposure to glyphosate technical). No publicly-available information was located regarding the effects of inhaled glyphosate or glyphosate-containing products. Limited animal data for dermal exposure to glyphosate technical indicate that glyphosate is not a dermal irritant. Results from the oral animal studies identify the following targets of glyphosate toxicity, albeit at relatively high dose levels:

- **Gastrointestinal effects:** Clinical signs and/or pathological evidence of glyphosate-induced irritation were observed in several animal studies; the lowest dose level resulting in gastrointestinal effects was 350 mg/kg/day. Gastrointestinal disturbances are signs and/or symptoms following ingestion of large amounts of glyphosate-containing products.

- **Developmental effects:** Glyphosate treatment-related developmental effects were noted in a few studies at dose levels (≥1,234 mg/kg/day) resulting in maternal toxicity as well.

- **Body weight effects:** Depressed body weight and/or body weight gain resulted from repeated dosing of glyphosate technical at dose levels ≥1,183 mg/kg/day.

- **Hepatic effects:** Increases in liver weight and serum ALT activity were observed in one repeated-dose study at a dose level of 1,678 mg/kg/day.

- **Ocular effects:** Lens abnormalities were observed in one repeated-dose study at a dose level of 940 mg/kg/day.

- **Renal effects:** Indicators of renal toxicity were noted in rats and mice administered glyphosate technical in the diet for 2 years at high doses (940 and 6,069 mg/kg/day, respectively).

- **Other effects:** Neurological, hematological, immunological, and reproductive endpoints have been evaluated, but do not appear to be particular targets of glyphosate toxicity.

- **Cancer**: Glyphosate is presently being re-evaluated for potential to cause cancer.

An overview of the number of human and animal studies examining potential endpoints of concern from exposure to glyphosate formulations is presented in Figure 2-2. Results from available animal studies identify the following targets of toxicity:

- **Developmental effects:** Histopathologic testicular lesions, decreased sperm production, and increased incidence of fetal skeletal malformations were reported in response to oral dosing of rat weanlings or pregnant rats with selected glyphosate formulations in the range of 5–500 mg/kg/day.

- **Endocrine effects:** Decreased serum testosterone was noted in male rat weanlings administered a glyphosate formulation orally at 5 mg/kg/day.

- **Body weight effects:** Seriously depressed body weight gain resulted was observed in mice administered a glyphosate formulation orally at 50 mg/kg/day.

- **Renal effects:** Histopathologic kidney lesions were noted in male rats gavaged once with a glyphosate formulation at 250 mg/kg.

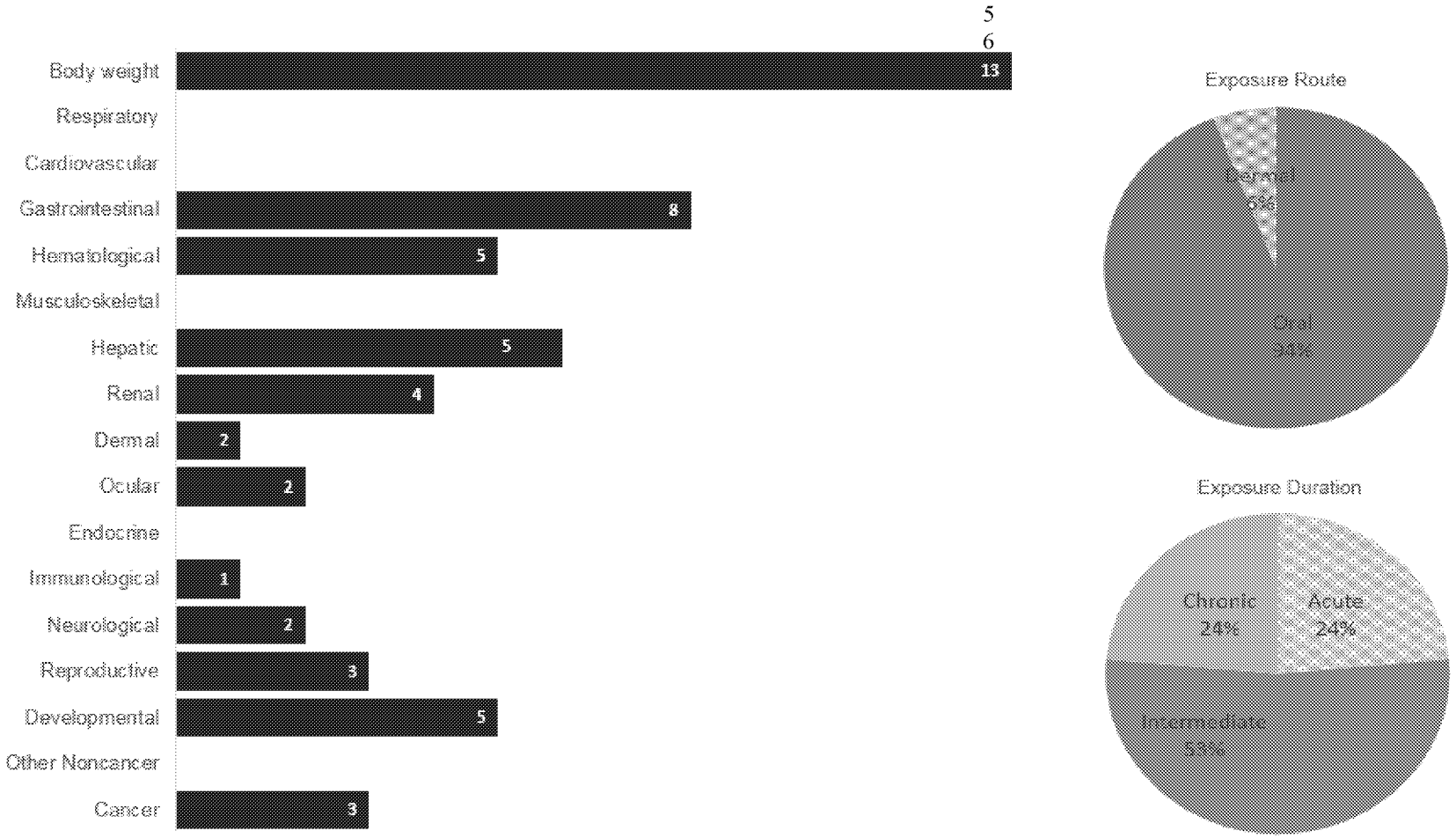
- **Hepatic effects:** Increased serum liver enzyme activity and histopathologic liver lesions were reported in male rats repeatedly gavaged with a glyphosate formulation at 487 mg/kg/day.

- **Hematological effects:** Decreases in red blood cells, hematocrit, and hemoglobin, and increases in mean corpuscular volume and neutrophils were reported in mice administered a glyphosate formulation orally at 500 mg/kg/day.

- **Reproductive effects:** Increased percentage of morphologically abnormal sperm was reported among rats receiving a glyphosate formulation from the drinking water for 8 days at 640 mg/kg/day.

Figure 2-1. Overview of the Number of Animal Studies Examining Glyphosate Technical Health Effects*

Most studies examined the potential body weight, gastrointestinal, hematological, hepatic, and developmental effects of glyphosate technical

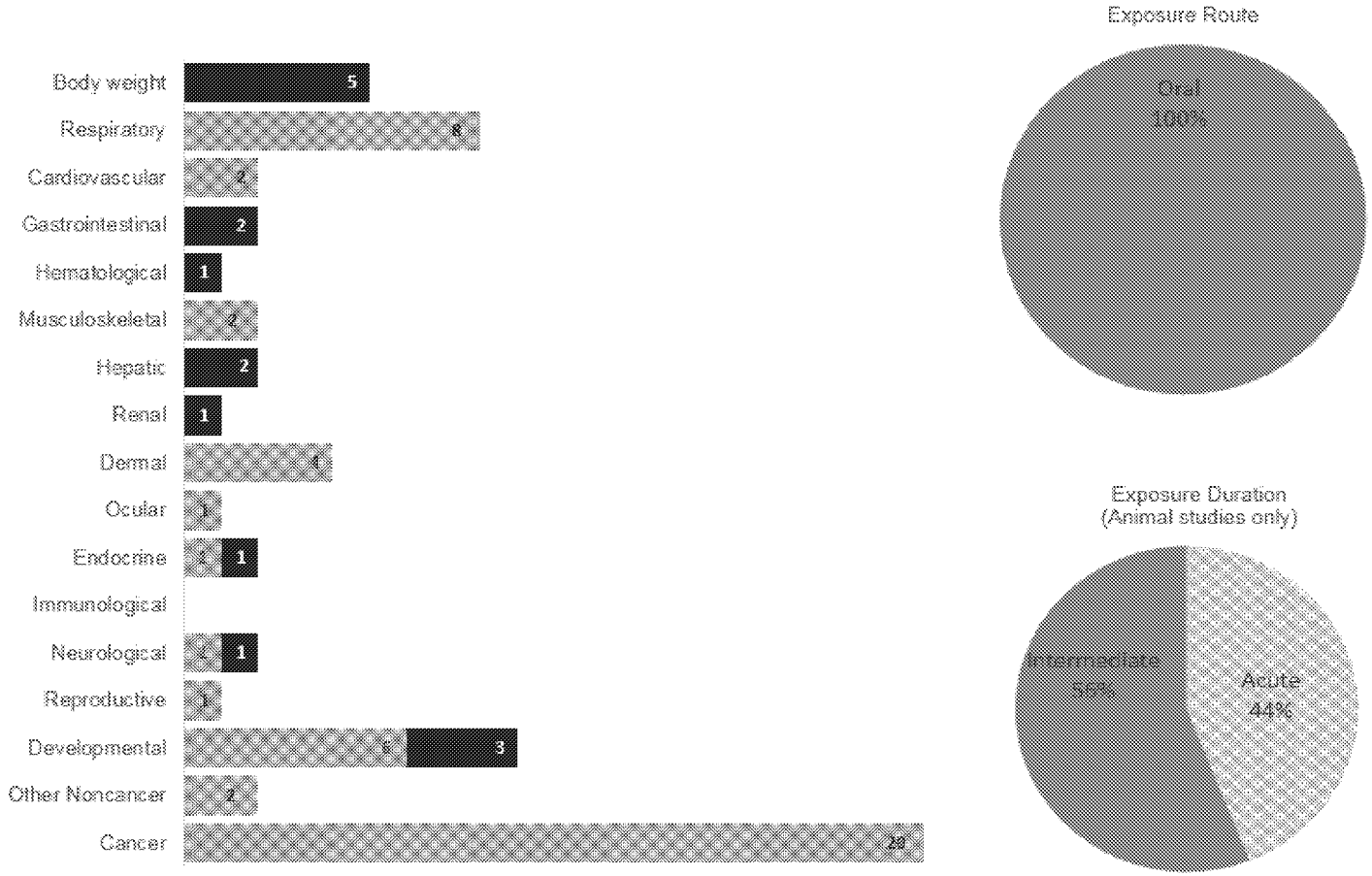


*Includes only publicly available animal studies that employed oral exposure to glyphosate technical as discussed in Chapter 2. A total of 17 studies include those finding no effect. Most studies examined multiple endpoints.

Figure 2-2. Overview of the Number of Studies Examining Glyphosate Formulations Health Effects*

Most studies examined the potential body weight, respiratory, dermal, developmental and cancer effects of glyphosate technical

More studies evaluated health effects in humans than **animals** (counts represent studies examining endpoint)



*A total of 30 studies include those finding no effect. Many studies examined multiple endpoints. Exposure to humans was assumed to be by inhalation. Exposure duration information was not available for humans. Therefore, exposure duration is plotted only for animal studies.

Table 2-1. Levels of Significant Exposure to Glyphosate Technical – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (Wistar) 8 M	Once (G)	0, 3,000	CS, GN, HP, LE, OW	Gastro		3,000		Diarrhea in 2/8 rats for 6 hours postdosing, resolving by sacrifice at 24 hours
Adam et al. 1997 – Glyphosate technical, purity not specified									
2	Rat (Sprague-Dawley) 5 (mixed)	Once (GW)	3,160, 3,980, 5,010, 6,310	CS, GN, LE	Death			4,320	LD_{50}
EPA 1992b – Glyphosate technical, purity not specified									
3	Rat (Sprague-Dawley) 25 F	GDs 6–19 1 x/d (GW)	0, 300, 1,000, 3,500	BW, CS, DX, FX, GN, LE, MX, TG	Death			3,500	6/25 Dams died
					Bd Wt	1,000		3,500	28.5% depressed mean body weight
					Gastro	1,000		3,500	Diarrhea, soft stools
					Develop	1,000	3,500		9% depressed mean fetal body weight, increased incidence of unossified sternebrae at serious maternally-toxic dose level
EPA 1992e – Glyphosate technical, purity 98.7%									
4	Rat (Alpk: APfSD) 10 M, 10 F	Once (GW)	0, 500, 1,000, 2,000	BW, CS, FI, GN, HP, LE, OF, OW	Neuro	2,000			
EPA 2013c – Glyphosate technical, purity 95.6%									

Table 2-1. Levels of Significant Exposure to Glyphosate Technical – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
INTERMEDIATE EXPOSURE									
5	Rat (Sprague-Dawley) 30 M, 30 F	2-Generation study, up to 19 wk/ generation (F)	F0 M: 0, 137, 754, 2,219 F0 F: 0, 160, 802, 3,134 F1 M: 0, 165, 818, 2,633 F1 F: 0, 194, 947, 3,035	NS	Bd Wt	754 M	2,219 M		Up to 12% depressed mean body weight gain
						802 F	3,134 F		Up to 18% depressed mean body weight gain
					Gastro	754 M	2,219 M		Soft stool
						802 F	3,134 F		Soft stool
					Repro	2,219 M 3,134 F			
					Develop	802	3,134		Up to 14–20% depressed mean pup body weight or body weight gain during lactation at maternally-toxic dose level
EPA 1992a – Glyphosate technical, purity 97.67%									
6	Rabbit (Dutch belted) 16 F	GDs 6–27 1 x/d (GW)	0, 75, 175, 350	BW, CS, DX, FX, GN, LE, MX, TG	Death			350	10/16 maternal rabbits died
					Bd Wt	350			
					Gastro	175	350		Increased incidence of soft stool and/or diarrhea
					Develop	350			
EPA 1992f – Glyphosate technical, purity 98.7%									
7	Rat (Sprague-Dawley) 12 M, 24 F	3-Generation study (F)	0, 3, 10, 30	BW, CS, DX, FI, FX, GN, HP, LE, MX, OW	Bd Wt	30			
					Repro	30			
					Develop	30			
EPA 1992g – Glyphosate technical, purity 98.7%									

Table 2-1. Levels of Significant Exposure to Glyphosate Technical – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
8	Rat (Sprague-Dawley) 28 M, 28 F	2-Generation study, up to 19 wk/ generation (F)	M: 0, 121, 408, 1,234; F: 0, 126, 423, 1,273	BW, CS, DX, FI, FX, GN, HP, LE, MX, OF, OW, TG	Bd Wt	1,234 M 1,273 F			
					Hepatic	1,234 M 1,273 F			
					Renal	1,234 M 1,273 F			
					Repro	1,234 M 1,273 F			
					Develop	408 M	1,234 M		Delayed preputial separation
EPA 2013a – Glyphosate technical, purity 95.7%									
9	Mouse (B6C3F1/ Crl) 10 F	28 d (F)	0, 150.1, 449.1, 1,447.5	BW, CS, FI, GN, OF, OW, WI	Bd Wt	1,447.5			
					Immuno	1,447.5			
EPA 2013b – Glyphosate technical, purity 82.5%									
10	Rat (Alpk: APfSD) 12 M, 12 F	13 wk (F)	M: 0, 155.5, 617.1, 1,546.5 F: 0, 166.3, 672.1, 1,630.6	BW, CS, FI, GN, HP, LE, OF, OW	Neuro	1,546.5 M 1,630.6 F			
EPA 2013c – Glyphosate technical, purity 95.6%									

Table 2-1. Levels of Significant Exposure to Glyphosate Technical – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
11	Rat (F344/N) 10 M, 10 F	13 wk (F)	M: 0, 205, 410, 811, 1,678, 3,393 F: 0, 213, 421, 844, 1,690, 3,393	BC, BW, CS, EA, FI, GN, HE, HP, LE, OF, OW	Bd Wt	1,678 M	3,393 M		18% lower mean body weight and body weight gain
						3,393 F			
					Gastro	1,678 M	3,393 M		Diarrhea
						1,690 F	3,393 F		Diarrhea
					Hemato	3,393			
					Hepatic	811 M	1,678 M		Increases in liver weight and serum ALT
						1,690 F	3,393 F		Increases in liver weight and serum AP, ALT, and bile acids
NTP 1992 – Glyphosate technical, purity 99%									
12	Mouse (B6C3F1) 10 M, 10 F	13 wk (F)	M: 0, 507, 1,065, 2,273, 4,776, 10,780 F: 0, 753, 1,411, 2,707, 5,846, 11,977	BW, CS, FI, GN, HP, LE, OF, OW	Bd Wt	2,273 M	4,776 M		11% lower mean final body weight
						5,846 F	11,977 F		10% lower mean final body weight
					Hepatic	10,780 M 11,977 F			
NTP 1992 – Glyphosate technical, purity 99%									

Table 2-1. Levels of Significant Exposure to Glyphosate Technical – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
13	Mouse (CD-1) 50 M, 50 F	24 mo (F)	M: 0, 161, 835, 4,945 F: 0, 195, 968, 6,069	BW, CS, FI, GN, HE, HP, LE	Bd Wt	4,945 M			
						6,069 F			
					Gastro	4,945 M			
						6,069 F			
					Hemato	4,945 M			
						6,069 F			
					Hepatic	835 M	4,945 M		Centrilobular hepatocellular necrosis
						6,069 F			
					Renal	4,945 M			
						968 F	6,069 F		Renal tubular epithelial basophilia
EPA 1985a, 1985b, 1986b, 1989, 1993, 2015a, 2016a – Glyphosate technical, purity 99.7%									
14	Dog (Beagle) 6 M, 6 F	1 yr (C)	0, 20, 100, 500	BC, BW, CS, FI, GN, HE, HP, LE, OP, OW, UR, WI	Bd Wt	500			
					Hemato	500			
					Ocular	500			
EPA 1986a, 1987 – Glyphosate technical, purity 96.13%									
15	Rat (Sprague-Dawley) 60 M, 60 F	Up to 24 mo (F)	M: 0, 89, 362, 940 F: 0, 113, 457, 1,183	BC, BW, CS, FI, GN, HE, HP, LE, OW	Bd Wt	940 M			
						457 F	1,183 F		13% lower mean body weight at treatment week 81
					Gastro	940 M			
						113 F	457 F		Inflammation of gastric squamous mucosa
					Hemato	940 M			
						1,183 F			

Table 2-1. Levels of Significant Exposure to Glyphosate Technical – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Hepatic	940 M			
						1,183 F			
					Renal	362 M	940 M		Increased specific gravity and decreased pH of urine
						1,183 F			
					Ocular	362 M	940 M		Increased incidence of lens abnormalities
						1,183 F			
EPA 1991a, 1991b – Glyphosate technical, purity 96.5%									
16	Rat (Sprague-Dawley) 50 M, 50 F	26 mo (F)	M: 0, 3.05, 10.30, 31.45 F: 0, 3.37, 11.22, 34.02	BC, BW, CS, FI, GN, HE, HP, LE, OF, OW, UR	Bd Wt	31.45 M			
						34.02 F			
					Gastro	31.45 M			
						34.02 F			
					Hemato	31.45 M			
						34.02 F			
					Hepatic	31.45 M			
						34.02 F			
					Renal	31.45 M			
						34.02 F			
EPA 1992d – Glyphosate technical, purity 98.7%									

[a]The number corresponds to entries in Figure 2-3.
ALT = alanine aminotransferase; AP alkaline phosphatase; BC = biochemistry; BW or Bd wt = body weight; C = capsule; CS = clinical signs; d = day(s); Develop = developmental; DX = developmental toxicity; EA = enzyme activity; (F) = exposure in feed; F = female(s); FI = food intake; FX = fetal toxicity; G = gavage, neat; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; GW = gavage in water vehicle; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; MX = maternal toxicity; mo = month(s); NOAEL = no observed-adverse-effect level; NS = not specified; OF = organ function; OP = ophthalmology; OW = organ weight; Repro = reproductive; TG = teratogenicity; UR = urinalysis; WI = water intake; wk = week(s); x = time; yr = year(s)

Figure 2-3. Levels of Significant Exposure to Glyphosate Technical – Oral
Acute (≤14 days)

Figure 2-3. Levels of Significant Exposure to Glyphosate Technical - Oral *(Continued)*

Intermediate (15-364 days)

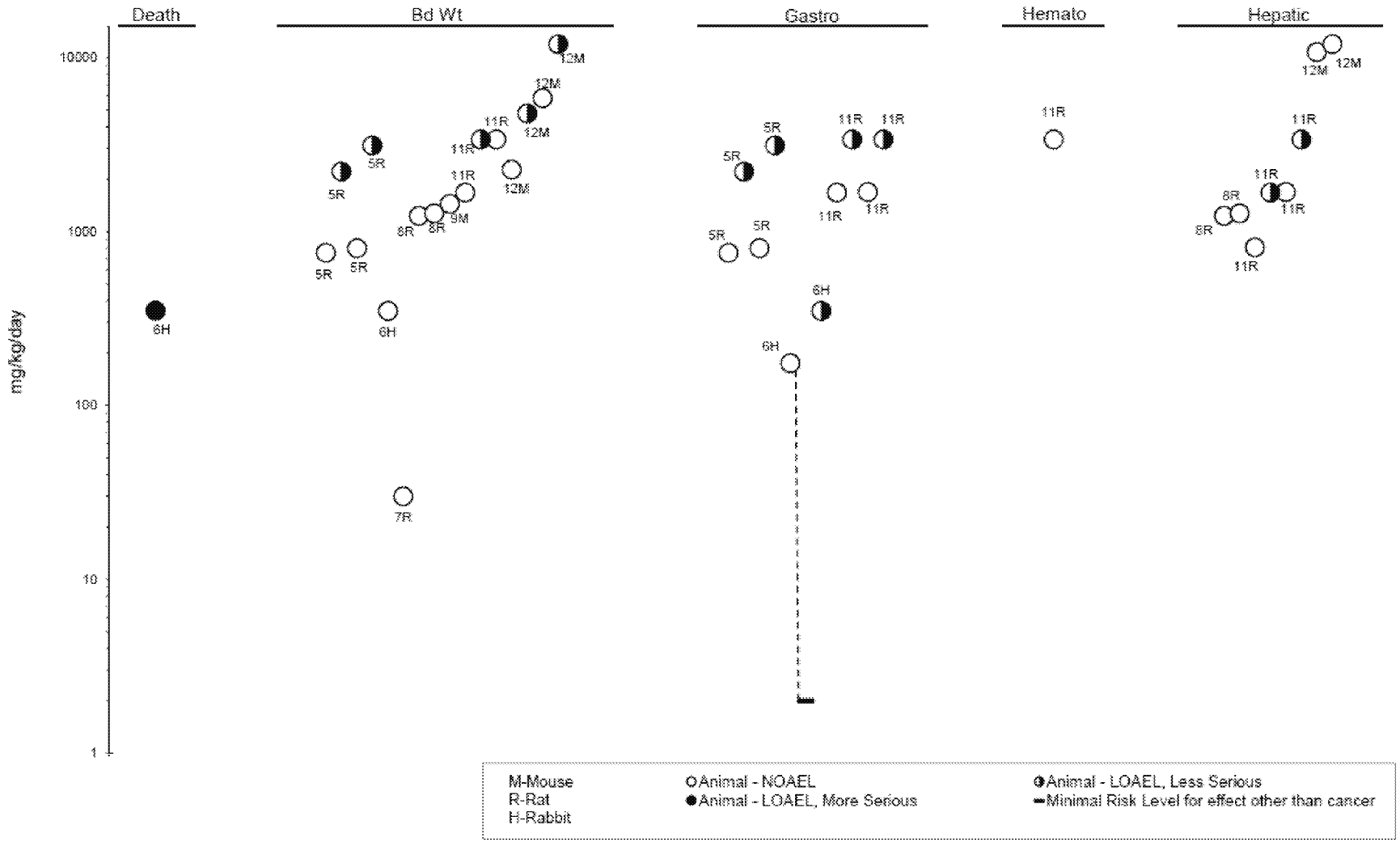


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Figure 2-3. Levels of Significant Exposure to Glyphosate Technical - Oral *(Continued)*

Intermediate (15-364 days)

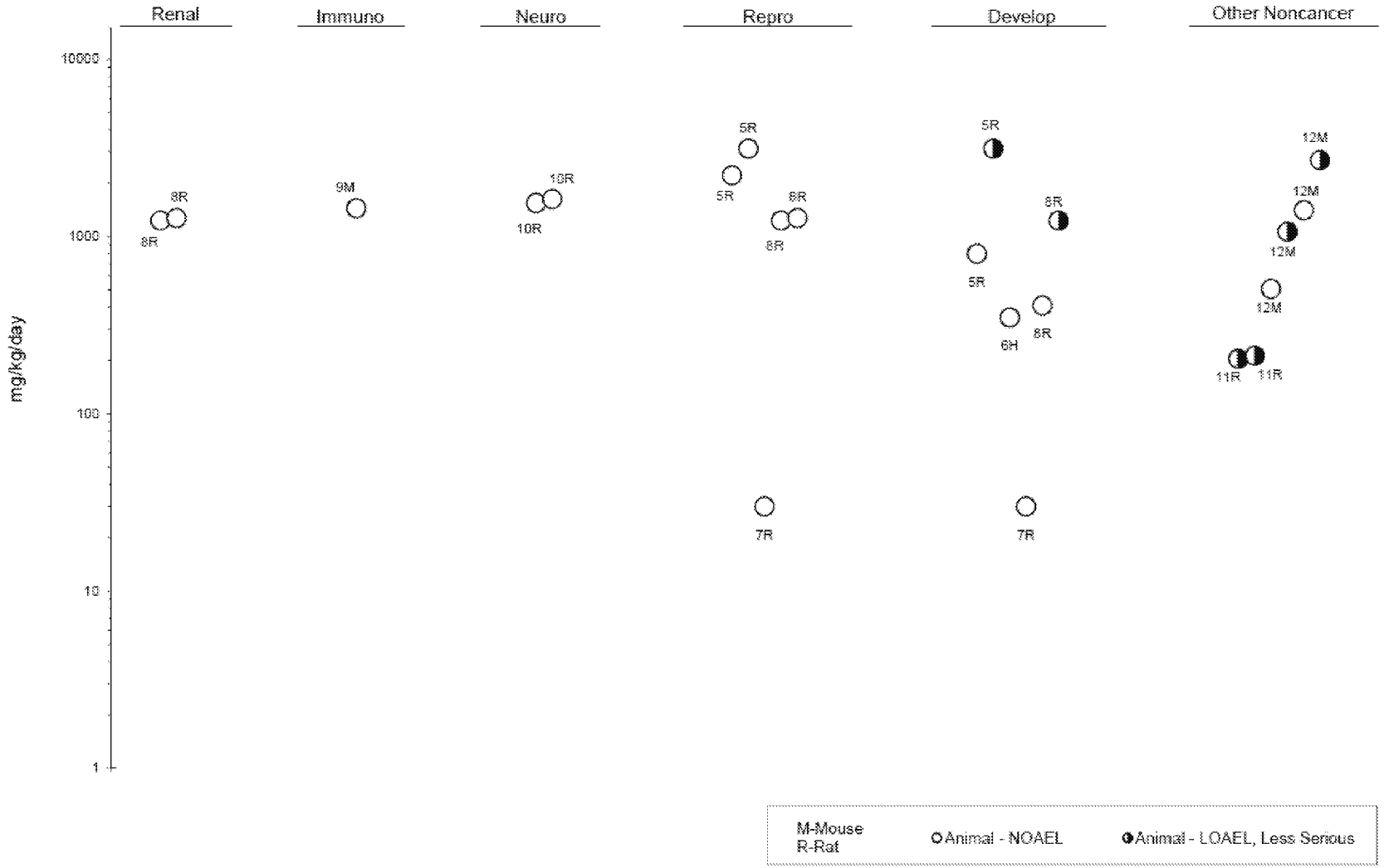

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Figure 2-3. Levels of Significant Exposure to Glyphosate Technical - Oral *(Continued)*

Chronic (≥365 days)

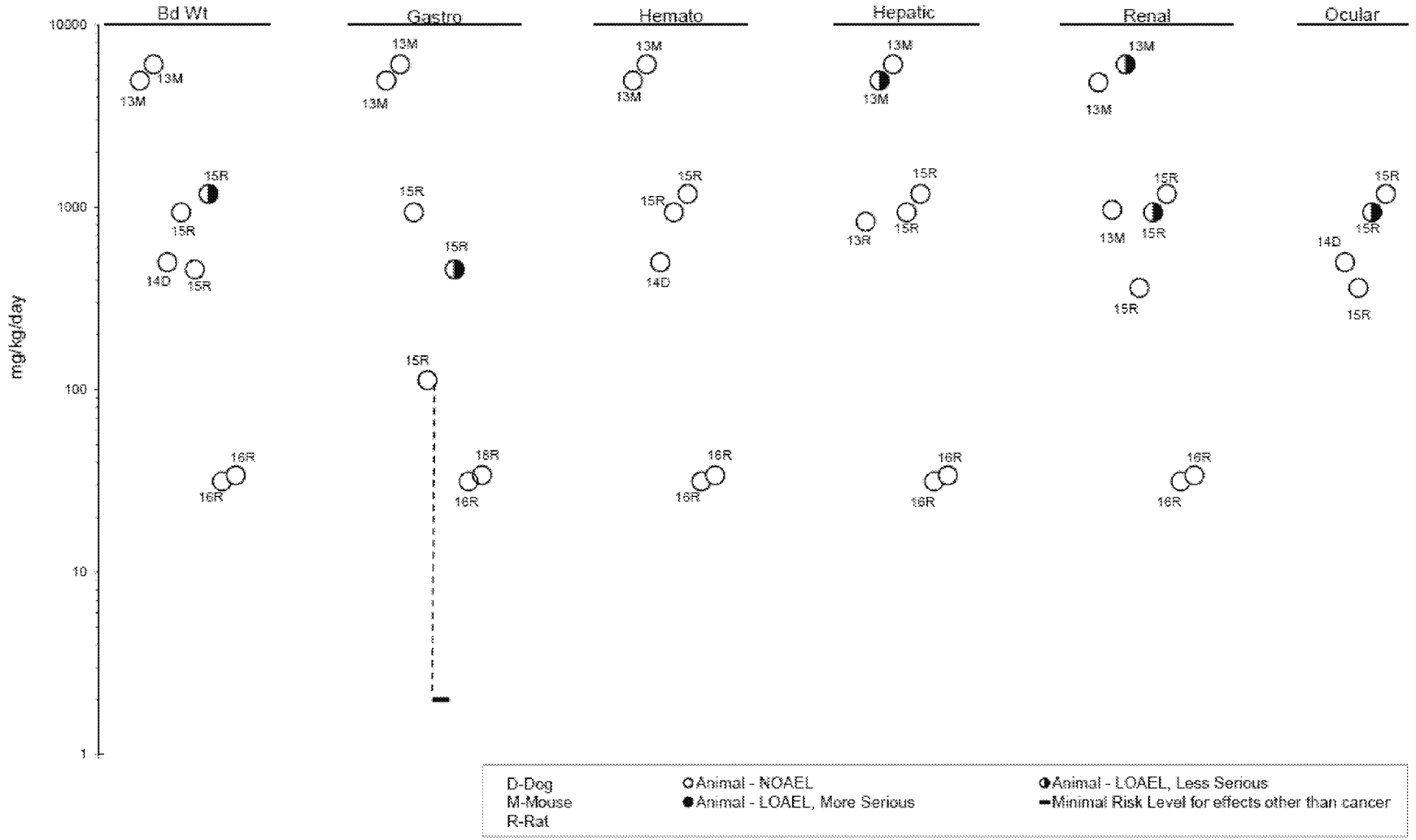

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Table 2-2. Levels of Significant Exposure to Glyphosate Formulations – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (Wistar) 8 M	Once (G)	0, 3,000	CS, GN, HP, LE, OW	Gastro			3,000	Diarrhea in rats administered Roundup or glyphosate + POEA at the same concentrations as contained in the Roundup formulation
Adam et al. 1997 – 41% w/v glyphosate isopropylamine salt (equivalent to 360 g/L glyphosate) and 18% POEA surfactant									
2	Rat (Sprague-Dawley) 15 M	8 d (W)	0, 640	BW, OF, OW, WI	Repro		640		Up to 18% increased percent abnormal sperm morphology;
Cassault-Meyer et al. 2014 – Roundup Grand Test substance: Travaux Plus (450 g/L glyphosate, 90 g/L ethoxylated etheralkylamine surfactant)									
3	Rat (Wistar) 15 F	GDs 6–15, 1 x/d (GW)	0, 500, 750, 1,000	BW, DX, FI, FX, GN, HP, LE, MX, OW, TG, WI	Death			1,000 F	8/15 dams died
					Bd Wt	1,000 F			
					Develop		500		Increased incidence of fetal skeletal malformations
Dallegrave et al. 2003 – Roundup (Monsanto of Brazil; 360 g/L glyphosate, 18% w/v polyoxyethyleneamine surfactant).									
4	Rat (Wistar) 4 M	Once (GW)	0, 250, 500, 1,200, 2,500	HP, OF	Renal		250 M		Histopathologic kidney lesions.
Wunnapuk et al. 2014 – Concentrate Roundup Weedkiller, Monsanto Australia containing 360 g/L of glyphosate (only ingredient specified in report)									
INTERMEDIATE EXPOSURE									
5	Rat (Wistar) 14 or 16 M	75 d, 1 x/2 d (GW)	0, 4.87, 48.7, 487	EA, OF	Hepatic	48.7 M	487 M		Increased serum liver enzyme activity, histopathologic liver lesions
Benedetti et al. 2004 – Glyphosate-Biocarb (360 g/L glyphosate and 18% w/v polyoxyetheleneamine surfactant)									

Table 2-2. Levels of Significant Exposure to Glyphosate Formulations – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
6	Rat (Wistar) NS	5 wk, 1 x/d (GW)	0, 56, 560	BW, EA, FI, HE, HP, OF, OW, WI	Bd Wt	560			
					Hepatic	560			
Caglar and Kolankaya 2008 – Roundup (Monsanto of Brazil; 360 g/L glyphosate and 18% w/v polyoxyethyleneamine surfactant)									
7	Rat (Wistar) NS	13 wk, 1 x/d (GW)	0, 56, 560	BW, EA, FI, HE, HP, OF, OW, WI	Bd Wt	560			
					Hepatic	560			
Caglar and Kolankaya 2008 – Roundup (Monsanto of Brazil; 360 g/L glyphosate and 18% w/v polyoxyethyleneamine surfactant)									
8	Rat (Wistar) 15 F	42–44 d (gestation, lactation) (GW)	0, 50, 150, 450	BW, CS, DX, FX, HP, LE, MX, OW, TG	Bd Wt	450 F			
					Develop			50 M	Decreased sperm production, histopathologic testicular lesions
Dallegrave et al. 2007 – 360 g/L glyphosate, 18% w/v polyoxyethyleneamine surfactant									
9	Mouse (albino Swiss) 10 M, 10 F	15 d 1 x/d (GW)	0, 50, 500	BW, EA, HE, HP, OF	Bd Wt			50	60–66% depressed mean body weight gain
					Hemato	50		500	Decreased red blood cells, hematocrit, hemoglobin; increased mean corpuscular volume, neutrophils
					Hepatic	500			
Jasper et al. 2012 – Monsanto Roundup Original containing 41% glyphosate and 16% polyethoxyleneamine surfactant									

Table 2-2. Levels of Significant Exposure to Glyphosate Formulations – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
10	Rat (Wistar) 16–18 M	30 d, (PPDs 23–53) (GW)	0, 5, 50, 250	BW, DX, HP, OF, OW	Bd Wt	250 M			
					Endocr		5 M		Decreased serum testosterone.
					Develop		5 M		Decreased epithelial thickness and increased luminal diameter in seminiferous tubules

Romano et al. 2010 – Roundup Transorb (648 g/L isopropylamine salt of glyphosate and 594 g/L inerts)

[a]The number corresponds to entries in Figure 2-4.

Bd Wt or BW = body weight; CS = clinical signs; d = day; Develop = developmental; DX = developmental toxicity; EA = enzyme activity; Endocr = endocrine; F = female(s); FI = food intake; FX = fetal toxicity; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; GW = gavage in water vehicle; HE = hematology; Hemato = hematological; HP = histopathology; IT = intratracheal; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MX = maternal toxicity; NOAEL = no observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; POEA = polyoxyethyleneamine; PPD = post-parturition day; Repro = reproductive; TG = teratogenicity; W = water vehicle; WI = water intake; wk = week(s); x = time

1

Figure 2-4. Levels of Significant Exposure to Glyphosate Formulations – Oral
Acute (≤14 days)

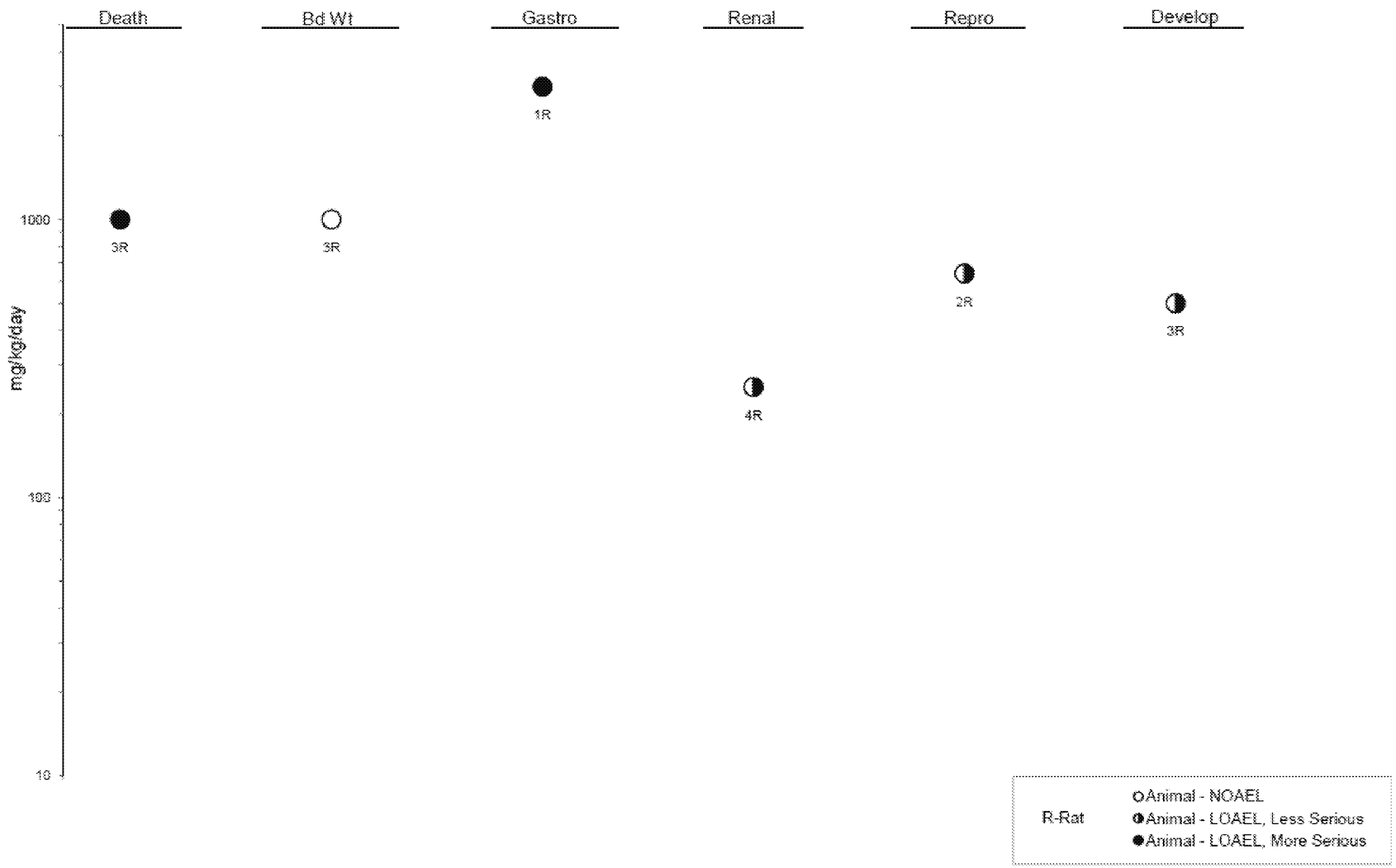

Figure 2-4. Levels of Significant Exposure to Glyphosate Formulations - Oral *(Continued)*

Intermediate (15-364 days)

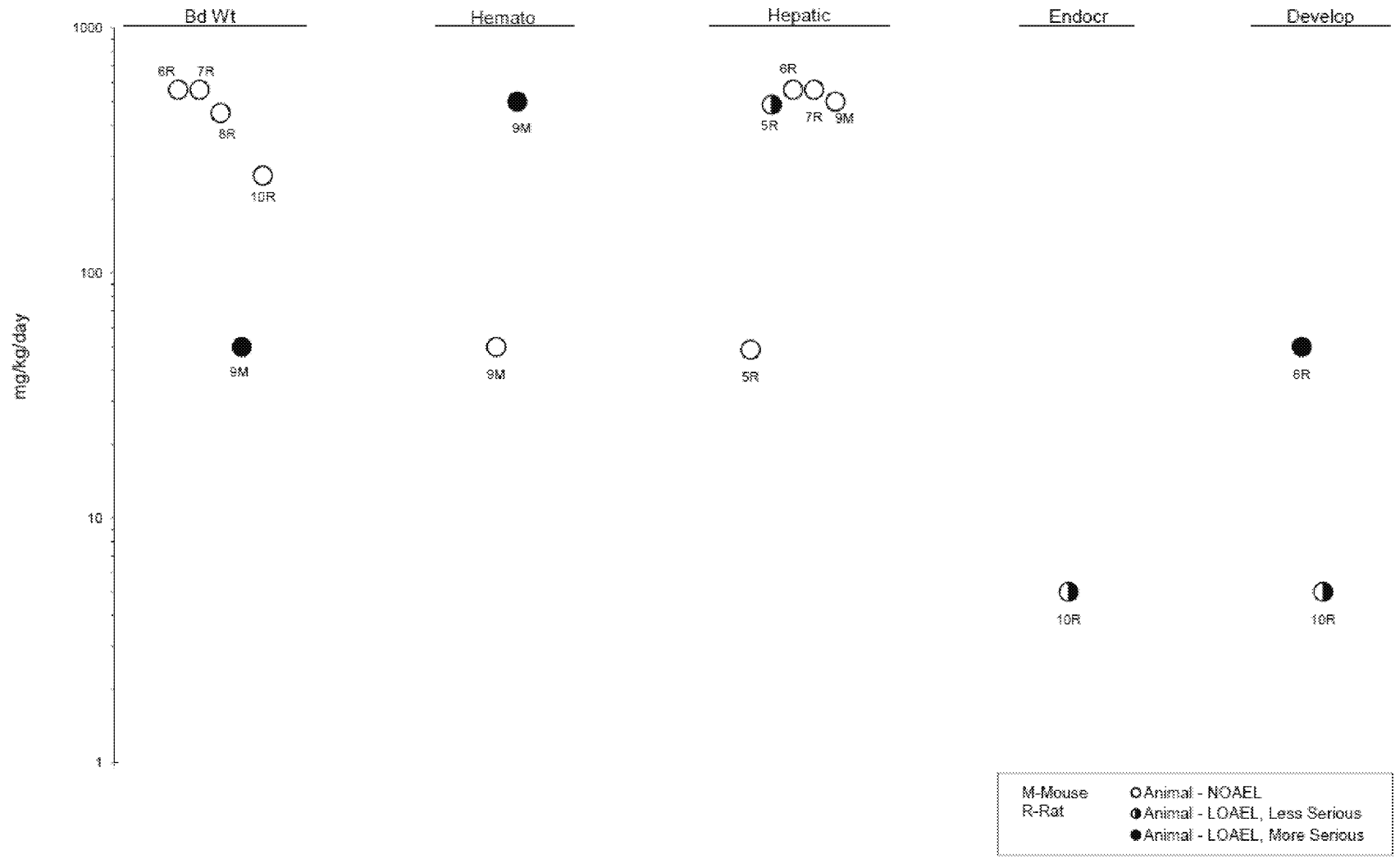

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Table 2-3. Levels of Significant Exposure to Glyphosate Technical – Dermal

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
INTERMEDIATE EXPOSURE								
Rabbit (New Zealand) 10 M, 10 F	21 d, 5 d/wk, 6 hr/d	0, 100, 1,000, 5,000	BC, BW, CS, EA, FI, GN, HE, HP, LE, OW	Bd Wt	5,000			
				Hemato	5,000			
				Hepatic	5,000			
				Dermal	1,000	5,000		Very slight erythema and edema at application site
EPA 1992c								
Glyphosate technical, purity not specified								

BC = biochemistry; BW or Bd wt = body weight; CS = clinical signs; EA = enzyme activity; F = female(s); FI = food intake; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no observed-adverse-effect level; OW = organ weight

1

2.2 DEATH

Several case report series have reported deaths in individuals intentionally ingesting glyphosate products (Chen et al. 2009; Kim et al. 2014; Roberts et al. 2010; Sawada et al. 1988; Talbot et al. 1991; Tominack et al. 1991). The predominant cause of death was often shock (hypovolemic or cardiogenic), hypotension, and respiratory failure, often due to aspiration (Chen et al. 2009; Kim et al. 2014; Talbot et al. 1991).

An acute oral LD_{50} value of 4,320 was reported following single oral dosing of rats with glyphosate technical (EPA 1992b). In a developmental toxicity study, 6/25 pregnant rats died during oral dosing of glyphosate technical at 3,500 mg/kg/day; there were no deaths during treatment at 1,000 mg/kg/day (EPA 1992e). No adequate publicly-available sources were located regarding death in laboratory animals exposed to glyphosate technical by inhalation or dermal routes.

In a study that employed oral dosing of pregnant rats with a glyphosate formulation, 8/15 dams died during the first 8 days of treatment at 1,000 mg/kg/day glyphosate (Dallegrave et al. 2003). No adequate publicly-available sources were located regarding death in laboratory animals exposed to glyphosate formulations by inhalation or dermal routes.

2.3 BODY WEIGHT

Oral exposure of rats to glyphosate technical at relatively high doses resulted in significant effects on body weight and/or body weight gain. Pregnant rats gavaged at 3,500 mg/kg/day during GDs 6–19 exhibited 28.5% lower mean body weight than controls (EPA 1992e). Body weight gain was 12–18% less than that of controls in two generations of parental male and female rats exposed via the diet for 14–19 weeks at 2,219 or 3,134 mg/kg/day, respectively (EPA 1992a). No treatment-related effects on body weight were seen among young female mice treated for 28 days at estimated doses up to 1,447.5 mg/kg/day (EPA 2013b). In 13-week oral studies, body weight and/or body weight gain among rats and mice at oral doses in the range of 2,273–11,977 mg/kg/day were 10–18% less than controls (NTP 1992). In a 2-year study, female rats dosed at 1,183 mg/kg/day exhibited 13% lower mean body weight than controls at treatment week 81 (EPA 1991a). There was no evidence of treatment-related effects on body weight among laboratory animals receiving oral doses of glyphosate technical at ≤1,000 mg/kg/day during acute-, intermediate-, or chronic-duration exposure (EPA 1986a, 1987, 1991a, 1991b, 1992a, 1992d, 1992e, 1992f, 1992g, 2013a, 2013b).

No significant treatment-related effects on body weight were observed among rabbits administered repeated dermal applications of glyphosate technical at doses in the range of 100–5,000 mg/kg/application for 21 days (EPA 1992c).

Several studies evaluated effects of oral exposure to glyphosate formulations on body weight. Limited results indicate that mice may be more sensitive than rats to body weight effects from repeated oral exposure to glyphosate formulations. Seriously-depressed mean body weight gain (60–66% less than controls) was reported for albino Swiss mice gavaged at 50 mg/kg/day for 15 days and approximately 10% body weight loss for mice dosed at 500 mg/kg/day (Jasper et al. 2012). No significant effects on body weight were observed among Wistar rats gavaged at 56 or 560 mg/kg/day for up to 13 weeks (Caglar and Kolankaya 2008), pregnant Wistar rats gavaged at 1,000 mg/kg/day during GDs 6–15 (Dallegrave et al. 2003), or maternal Wistar rats gavaged at 50–450 mg/kg/day during gestation and lactation (Dallegrave et al. 2007). No effects on body weight were observed among male Wistar rats gavaged at 250 mg/kg/day during postnatal days (PNDs) 23–53 (Romano et al. 2010).

2.4 RESPIRATORY

As summarized in Table 2-4, several investigations of the Agricultural Health Study participants have examined the possible associations between glyphosate use and increased risk of rhinitis, wheezing, atopic asthma, allergic asthma, or chronic bronchitis (Hoppin et al. 2002, 2006a, 2006b, 2007, 2008, 2009; Slager et al. 2009, 2010). No associations were found for diagnosed chronic bronchitis (Hoppin et al. 2007) or for wheezing after adjusting for confounding exposure to other pesticides (Hoppin et al. 2002, 2006a, 2006b). Current rhinitis was associated with glyphosate use among commercial applicators (Slager et al. 2009) and farmers (Slager et al. 2010), but no relationship between risk and the number of days of use per year was found among the commercial applicators (Slager et al. 2009). An association between glyphosate use and the risk of atopic asthma was found among farm women, but there was no association with nonatopic asthma (Hoppin et al. 2008). No associations were found between glyphosate use by male farmers and risk of allergic or nonallergic asthma (Hoppin et al. 2009). It is noted that most of these studies did not account for other pesticide uses. Respiratory failure or distress was reported in about 10–25% of the cases of intentional ingestion of glyphosate products (Lee et al. 2000; Moon and Chun 2010; Tominack et al. 1991).

Table 2-4. Noncancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
Respiratory		
Hoppin et al. 2002 Cohort study of 20,468 participants in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any glyphosate exposure and application frequency categories **Logistic regression adjustments:** age, state, smoking history, asthma-atopy status	Wheeze, self-reported OR 1.05 (0.95–1.17), p=0.04 for trend of increasing exposure days
Hoppin et al. 2006a Prospective cohort study of 20,175 participants in the Agricultural Health Study in Iowa and North Carolina (17,920 farmers and 2,255 commercial pesticide applicators)	**Exposure:** any glyphosate exposure **Logistic regression adjustments:** age, state, smoking history, BMI	Wheeze, self-reported OR 1.05 (0.94–1.17), farmers OR 1.14 (0.83–1.57), applicators
Hoppin et al. 2006b Cohort study of 2,255 commercial pesticide applicators participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any glyphosate exposure **Logistic regression adjustments:** age, smoking status, asthma and atopy history, BMI	Wheeze, self-reported OR 1.38 (1.03–1.86) OR 1.14 (0.83–1.57), with adjustment for use of chlorimuron-ethyl pesticide
Hoppin et al. 2007 Prospective cohort study of 20,908 participants in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any glyphosate exposure **Logistic regression adjustments:** age, state, sex, pack years	Chronic bronchitis OR 0.99 (0.82–1.19)
Hoppin et al. 2008 Prospective cohort study of 25,814 farm women participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any glyphosate exposure **Logistic regression adjustments:** age, state, smoking status, "grew up on farm"	Atopic asthma OR 1.31 (1.02–1.67) Nonatopic asthma OR 1.13 (0.92–1.39)
Hoppin et al. 2009 Prospective cohort study of 19,704 male farmers participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any glyphosate exposure **Logistic regression adjustments:** age, state, smoking status, BMI	Allergic asthma OR 1.37 (0.86–2.17) Nonallergic asthma OR 1.15 (0.87–1.51)

Table 2-4. Noncancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
Slager et al. 2009 Prospective cohort study of 2,245 commercial applicators participating in the Agricultural Health Study in Iowa	**Exposure:** any glyphosate exposure and application frequency categories **Logistic regression adjustments:** age, education, "growing up on farm"	Current rhinitis OR 1.32 (1.08–1.61), p=0.735 for trend for increasing use days per year
Slager et al. 2010 Prospective cohort study of 19,565 farmers participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any glyphosate exposure and application frequency categories **Logistic regression adjustments:** age; race; education; state; BMI; currently working on farm; years mixing pesticides, repairing engines or pesticide equipment, welding, painting, handling stored grain or hay, working in swine areas, working with hogs or other farm animals, butchering animals, and growing cabbage, Christmas trees, field corn, sweet corn, and hay	Current rhinitis OR 1.09 (1.05–1.13)
Cardiovascular Effects		
Dayton et al. 2010 Case control study of 168 cases of nonfatal myocardial infarction and 22,257 controls in women in Iowa and North Carolina participating in the Agricultural Health Study	**Exposure:** any glyphosate exposure **Logistic regression adjustments:** age, BMI, smoking, state	Nonfatal myocardial infarction OR 0.8 (0.6–1.2)
Mills et al. 2009 Prospective study of male participants in the Agricultural Health Study in Iowa and North Carolina (n=54,069 for fatal myocardial infarction and 32,024 for nonfatal incidence)	**Exposure:** any glyphosate exposure **Cox proportional regression adjustments:** age, state, smoking, BMI (nonfatal analysis only)	Fatal myocardial infarction HR 0.99 (0.80–1.23) Nonfatal myocardial infarction HR 1.10 (0.93–1.31)

Table 2-4. Noncancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
Musculoskeletal Effects		
De Roos et al. 2005b Nested case control study of 135 cases of physician-confirmed rheumatoid arthritis and 675 controls participating in the Agricultural Health Study in Iowa and North Carolina (female participants only)	**Exposure:** any glyphosate exposure **Unconditional logistic regression adjustments:** birth date, state	Rheumatoid arthritis OR 1.2 (0.8–1.8)
Dermal Effects		
Maibach 1986 Experimental study of 24 males and females	**Exposure:** 0.1 mL applied to intact and Draize-type abraded skin; patch removed after 24 hours	No skin irritation 24 or 48 hours after application to intact skin Irritancy scores 24 hours after application to abraded skin were negative in 10 subjects, equivocal in 4 subjects and erythema was noted in 10 subjects; at 48 hours, the scores were negative in 10 subjects, equivocal in 6 subjects, and erythema was noted in 8 subjects
Maibach 1986 Experimental study of 23 males and females	**Exposure:** 0.1 mL applied 5 days/week for 21 days	The average score was 1.4 where a score of 1 indicates erythema and 2 indicates erythema and induration; none of the subjects reported burning, stinging, or itching from the test compound
Maibach 1986 Experimental study of 204 males and females	**Exposure:** 0.2 mL applied to 3 days/week for 3 weeks with patches remaining in place for 48–72 hours; a challenge patch was applied after a 2-week rest period	No skin irritation was observed
Maibach 1986 Experimental study of 15 males and females	**Exposure:** Full-strength glyphosate was applied to skin stripped of the stratum corneum; the test site received irradiation with ultraviolet A and ultraviolet B light	No positive results for photoirritation or photosensitization were found

Table 2-4. Noncancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
Ocular Effects		
Kirrane et al. 2005 Prospective study of 31,173 female spouses of commercial pesticide applicators participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any glyphosate exposure **Hierarchial regression adjustments:** age, state	Retinal degeneration OR 1.1 (0.8–1.5)
Endocrine Effects		
Goldner et al. 2010 Prospective study of 16,529 participants (female spouses only) in the Agricultural Health Study in Iowa and North Carolina Thyroid disease was self-reported clinically diagnosed	**Exposure:** any glyphosate exposure **Polytomous logistic regression adjustments:** age, education, smoking status, hormone replacement therapy, BMI	Hyperthyroid disease OR 0.98 (0.78–1.2) Hypothyroid disease OR 1.0 (0.91–1.2) Other thyroid disease OR 0.97 (0.81–1.2)
Neurological Effects		
Kamel et al. 2007 Case control study of cases of self-reported Parkinson's disease (n=83 prevalent cases and 78 incident cases) and controls (n=79,557 prevalent controls and 55,931 incident controls) participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any glyphosate exposure **Logistic regression adjustments:** age, state, type of participant	Parkinson's disease OR 1.0 (0.6–1.7), prevalent disease OR 1.1 (0.6–2.0), incident disease Prevalent disease defined as reporting Parkinson's disease at enrollment and incident disease defined as Parkinson's disease reported at the study follow-up
Reproductive Effects		
Curtis et al. 1999 Retrospective cohort study of 2,012 planned pregnancies among participants in the Canadian Ontario Farm Family Health Study	**Exposure:** any glyphosate exposure **Cox proportional hazard adjustments:** age when beginning to try to conceive, recent oral contraceptive use, men's and women's smoking, and use of other pesticides	Fecundability CFR 0.61 (0.30–1.26), pesticide use on the farm and women reported pesticide activities CFR 1.30 (1.07–1.56), pesticide use on the farm, but no pesticide activities reported by women

Table 2-4. Noncancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
Developmental Effects		
Arbuckle et al. 2001 Retrospective cohort study of 2,110 female participants in the Canadian Ontario Farm Family Health Study	**Exposure:** any glyphosate exposure **Logistic regression adjustments:** none	Spontaneous abortion, preconception exposure OR 1.4 (1.0–2.1), all gestational ages OR 1.1 (0.7–1.9), <12 weeks gestation OR 1.7 (1.0–2.9), >12 weeks gestation Spontaneous abortion, postconception exposure OR 1.1 (0.7–1.7), all gestational ages OR 0.8 (0.4–1.6), <12 weeks gestation OR 1.4 (0.8–2.5), >12 weeks gestation
Garcia et al. 1998 Case control study of 261cases of congenital malformations and 261 matched controls in Spain	**Exposure:** any paternal glyphosate exposure **Conditional logistic regression adjustments:** paternal age and paternal job and maternal history of spontaneous abortion, twins, drug consumption, heavy smoking, education, occupation	Congenital malformations OR 0.94 (0.37–2.34)
Garry et al. 2002 Cross sectional study of 695 families and 1,532 children in Minnesota	**Exposure:** any glyphosate exposure **Regression adjustments:** maternal age, smoking status, alcohol use, season of conception	ADD/ADHD, parent reported OR 3.6 (1.35–9.65)
Rull et al. 2006 Case control study of 731 cases of neural tube defects and 940 controls in California	**Exposure:** maternal residential proximity of 1,000 m of glyphosate application **Unconditional logistic regression adjustments:** maternal ethnicity, education, periconceptional smoking, vitamin use	Neural tube defects OR 1.5 (1.0–2.4) OR 1.5 (0.8–2.9) with adjustment for other pesticide exposure

Table 2-4. Noncancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
Sathyanarayana et al. 2010 Prospective study of 2,246 women whose most recent singleton birth occurred within 5 years of enrollment in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any maternal glyphosate exposure **Linear regression adjustments:** maternal BMI and height, parity, preterm status, state, maternal smoking during pregnancy	Birth weight, change β 4 g (-40–48 g)
Savitz et al. 1997 Retrospective cohort study of 1,898 couples participating in the Canadian Ontario Farm Family Health Study	**Exposure:** any paternal glyphosate exposure **Logistic regression adjustments:** maternal age, parity, maternal and paternal education, income, maternal and paternal off farm job, maternal smoking and alcohol use during pregnancy, conception to interview interval	Miscarriage OR 1.5 (0.8–2.7) Preterm delivery OR 2.4 (0.8–7.9) Small for gestational age OR 0.8 (0.2–2.3)
Other Noncancer Effects		
Montgomery et al. 2008 Prospective study of 33,457 participants (white males only) in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any glyphosate exposure **Logistic regression adjustments:** age, state, BMI	Diabetes incidence OR 0.85 (0.74–0.98)
Saldana et al. 2007 Prospective study of 11,273 participants in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any glyphosate exposure during the first trimester **Unconditional logistic regression adjustments:** BMI at enrollment, mother's age at pregnancy, parity, race, state, commonly used pesticides by women	Gestational diabetes mellitus OR 0.7 (0.2–1.75)

ADD/ADHD = attention deficit disorder/attention deficit hyperactivity disorder; BMI = body mass index; CFR = conditional fecundability ratio; HR = hazard ratio; OR = odds ratio

1

Publicly-available data regarding respiratory effects in laboratory animals exposed to glyphosate are limited to results from a single study designed to evaluate the effects of glyphosate (200 mg/kg), glyphosate + polyoxyethyleneamine (POEA) (200 and 100 mg/kg, respectively), POEA alone (100 mg/kg), and a Roundup formulation (containing 200 mg glyphosate/kg and 100 mg POEA/kg) in rats evaluated for 24 hours following intratracheal instillation (Adam et al. 1997). Control rats received normal saline. Obvious clinical signs of adverse pulmonary effects and mortalities occurred in each group except the saline controls. The study authors stated that the pulmonary effects were more severe and lasted longer in rats treated with POEA alone or in combination with glyphosate compared to responses in glyphosate only-treated rats. These results suggest POEA was more acutely toxic than glyphosate to the lungs.

2.5 CARDIOVASCULAR

Two studies using Agricultural Health Study participants did not find associations between glyphosate use and the risk of myocardial infarctions (Dayton et al. 2010; Mills et al. 2009); see Table 2-4 for details. In case series reports, abnormal electrocardiogram (EKG) readings have been found in patients ingesting glyphosate (Kim et al. 2014; Lee et al. 2000, 2008; Moon and Chun 2010; Talbot et al. 1991). The most commonly reported alterations included prolonged QTc interval and sinus tachycardia. In the most severe poisoning cases, hypotension and shock have been reported (Roberts et al. 2010; Sawada et al. 1988; Tominack et al. 1991).

No data were located regarding cardiovascular effects in laboratory animals exposed to glyphosate technical or glyphosate formulations by any exposure route.

2.6 GASTROINTESTINAL

Gastrointestinal symptoms are commonly reported in case series reports of patients ingesting glyphosate products. In numerous reports, over 40% of the patients reported nausea/vomiting (Lee et al. 2000, 2008; Roberts et al. 2010; Sawada et al. 1988; Tominack et al. 1991). Other effects reported included abdominal pain (Lee et al. 2000, 2008; Moon and Chun 2010; Roberts et al. 2010; Sawada et al. 1988; Talbot et al. 1991), sore throat (Lee et al. 2000; Tominack et al. 1991), and damage to mucosal tissue in the mouth and esophagus (Chang et al. 1999; Sawada et al. 1988; Talbot et al. 1991; Tominack et al. 1991).

Several studies evaluated effects of glyphosate technical oral exposure in laboratory animals. The most common effect was clinical signs of gastrointestinal disturbances. Such clinical signs are commonly observed in studies of laboratory animals receiving bolus gavage doses of test substances, in which cases the clinical sign may be at least partially the result of the method of gavage dosing. Soft stool and/or diarrhea were reported among pregnant rats gavaged at 3,500 mg/kg/day during GDs 6–19 (EPA 1992e) and pregnant rabbits gavaged at 350 mg/kg/day during GDs 6–27 (EPA 1992f). In the rabbit study, a slight increase in observations of soft stool and/or diarrhea was noted at 175 mg/kg/day, but was not considered to represent a toxicologically significant effect. Soft stools were observed in rats exposed via the diet for 2 generations at concentrations resulting in estimated doses in the range of 2,219–2,633 and 3,035–3,134 mg/kg/day for parental males and females, respectively (EPA 1992a). In a 2-year study of rats exposed via the diet (EPA 1991a, 1991b), inflammation of gastric squamous mucosa was observed in females at an estimated dose level of 457 mg/kg/day; there were no signs of gastrointestinal effects in males at estimated doses as high as 940 mg/kg/day. In another chronic-duration oral rat study (EPA 1992d), there were no signs of treatment-related gastrointestinal effects at the highest estimated dose level (31.45–34.02 mg/kg/day). No clinical signs or histopathological evidence of treatment-related gastrointestinal effects were seen among male or female mice exposed via the diet for 24 months at estimated doses as high as 4,945–6,069 mg/kg/day (EPA 1985a).

Limited information was located regarding gastrointestinal effects in laboratory animals following oral exposure to glyphosate formulations. In one study, histopathologic lesions in stomach and pancreas were reported for rats treated by gavage for 8 weeks at 375 mg/kg/day; however, the study report did not contain quantitative incidence data, thus precluding independent evaluation. (Tizhe et al. 2014). Another study was designed to evaluate the effects of glyphosate (2,000 mg/kg), glyphosate + POEA (2,000 and 1,000 mg/kg, respectively), POEA alone (1,000 mg/kg), and a Roundup formulation (containing 2,000 mg glyphosate/kg and 1,000 mg POEA/kg) in rats evaluated for 24 hours following gavage administration (Adam et al. 1997). Control rats received normal saline. Two rats in the POEA-only treatment group died. Diarrhea was noted in all groups except the control group. The study authors stated that the groups given POEA or mixtures that included POEA experienced more rapid and severe diarrhea than those given glyphosate alone. These results suggest that POEA was more acutely toxic than glyphosate to the gastrointestinal system.

2.7 HEMATOLOGICAL

No information was located regarding hematological effects in humans exposed to glyphosate-containing products; results from available animal studies do not implicate the hematological system as a sensitive target of glyphosate toxicity. Hematological endpoints were evaluated in chronic-duration oral studies of rats (EPA 1991a, 1991b, 1992d), mice (EPA 1985a, 1993), and dogs (EPA 1986a, 1987) exposed to glyphosate technical. There were no apparent treatment-related effects in chronic-duration oral studies of rats, mice, or dogs administered glyphosate technical at oral doses as high as 940–1,183 mg/kg/day for rats (EPA 1991a, 1991b, 1992d), 4,945–6,069 mg/kg/day for mice (EPA 1985a, 1993), and 500 mg/kg/day for dogs (EPA 1986a, 1987). Rabbits administered repeated dermal applications of glyphosate technical at doses in the range of 100–5,000 mg/kg/application for 21 days exhibited no evidence of treatment-related hematological effects (EPA 1992c). Available information regarding hematological effects related to glyphosate formulations is limited to a report of decreases in red blood cell count, hematocrit, and hemoglobin, and increases in corpuscular volume and neutrophil count in mice gavaged for 15 days at 500 mg/kg/day (Jasper et al. 2012).

2.8 MUSCULOSKELETAL

In the only available epidemiology study examining potential musculoskeletal effects, De Roos et al. (2005b) did not find an association between glyphosate use and the risk of rheumatoid arthritis among participants of the Agricultural Health Study; see Table 2-4 for details.

No adequate publicly-available sources were located regarding musculoskeletal effects in laboratory animals exposed to glyphosate technical or glyphosate formulations by any exposure route.

2.9 HEPATIC

No information was located regarding hepatic effects in humans exposed to glyphosate-containing products. The potential for glyphosate technical to cause liver toxicity was evaluated in studies of rats and mice; there is some evidence that oral doses near or above recommended limit dosing for animal studies (2,000 mg/kg/day) may cause adverse liver effects. In a 13-week rat dietary study of glyphosate technical increases in liver weight and serum ALT were observed in males at 1,678 mg/kg/day; increased liver weight and increased serum AP, ALT, and bile acids were noted in females at 3,393 mg/kg/day. There were no indications of treatment-related liver effects among male and female rats treated via the diet for 2 generations at estimated doses as high as 1,234–1,273 mg/kg/day (EPA 2013a) or other rats

treated for 2 years to doses as high as 940–1,183 mg/kg/day (EPA 1991a, 1991b). Male mice exposed via the diet for 13 weeks at doses ≥2,273 mg/kg/day exhibited increased mean relative liver weight (4–9% greater than controls) in the absence of histopathologic liver lesions; there were no effects on liver weight in similarly-treated female mice at doses up to and including 11,977 mg/kg/day (NTP 1992). Male mice exposed via the diet for 2 years at an estimated dose of 4,945 mg/kg/day exhibited increased incidence of histopathologic central lobular hepatocyte necrosis; there was no evidence of treatment-related liver effects in similarly-treated female mice at an estimated dose of 6,069 mg/kg/day (EPA 1985a). Rabbits administered repeated dermal applications of glyphosate technical at doses in the range of 100–5,000 mg/kg/application for 21 days exhibited no evidence of treatment-related hepatic effects (EPA 1992c). Available information regarding hepatic endpoints in animals exposed to glyphosate formulations is limited to results from two studies. Increased serum ALT and aspartate aminotransferase (AST) activity and histopathologic liver lesions (increased Kupffer cells in hepatic sinusoids and deposition of reticulin fibers) in male rats treated by gavage for 75 days (one dose every 2 days) at 487 mg/kg/dosing (Benedetti et al. 2004). Tizhe et al. (2014) reported cellular degeneration and congestion in the liver of rats gavaged with a glyphosate formulation at 375 mg/kg/day for 8 weeks. However, the study report did not contain quantitative incidence data, thus precluding independent evaluation.

2.10 RENAL

One epidemiological study of glyphosate applicators found an increased risk of chronic kidney disease (Jayasumana et al. 2015). However, uncertainty regarding an association between exposure to glyphosate-containing products and risk of chronic kidney disease includes the finding that the applicators were also exposed to high levels of calcium, magnesium, barium, strontium, iron, titanium, and vanadium by drinking water from abandoned wells.

Several studies evaluated possible renal toxicity in laboratory animals treated with glyphosate technical. In a 2-generation reproductive toxicity study (EPA 2013a), slightly increased absolute and relative kidney weights (7–11% greater than controls) were reported among F0 parental female rats dosed at 1,273 mg/kg/day; there was no evidence of histopathologic kidney lesions. Therefore, the slightly increased kidney weight was not considered to represent a treatment-related adverse effect. During 2 years of dietary treatment of rats, urinalysis revealed increased specific gravity of urine and decreased urinary pH among males treated at an estimated dose of 940 mg/kg/day; there were no signs of treatment-related renal effects in urinalysis results from females treated at an estimated dose as high as 1,183 mg/kg/day (EPA 1991a, 1991b). Female mice treated for 2 years at an estimated dose of

6,069 mg/kg/day exhibited significantly increased incidence of renal proximal tubule epithelial basophilia and hypertrophy; there was no evidence of renal effects in similarly-treated male mice at an estimated dose of 4,945 mg/kg/day (EPA 1985a).

Information regarding renal effects in animals exposed to glyphosate formulations is restricted to results from two studies. There is some uncertainty regarding the role of glyphosate in the reported effects. Histopathologic kidney lesions (necrotic and apoptotic cells, localized primarily in tubular epithelium of the proximal straight tubule and thick ascending limb of the loop of Henle) were reported in male rats gavaged once with a glyphosate formulation at dose levels ranging from 250 to 2,500 mg/kg (Wunnapuk et al. 2014). Tizhe et al. (2014) reported glomerular degeneration and renal tubular necrosis with mononuclear cellular infiltration in the kidney of rats gavaged with a glyphosate formulation at 375 mg/kg/day for 8 weeks. However, the study report did not contain quantitative incidence data, thus precluding independent evaluation.

2.11 DERMAL

One study evaluated the potential dermal toxicity of glyphosate in humans. In an experimental study (see Table 2-4), a single application of glyphosate herbicide to intact skin for 24 hours did not result in irritation (Maibach 1986). When applied to abraded skin, erythema was noted in 42% of the subjects after 24 hours. Mild skin irritation was observed in a repeated exposure test study (Maibach 1986). No skin irritation was observed in a Draize skin sensitization test or in a photosensitivity/photoirritation test (Maibach 1986).

Available information regarding dermal effects in animals is limited to a few studies in which minor dermal irritation was reported in response to dermally-applied glyphosate technical. At the application site, very slight erythema and edema were observed in rabbits during 21 days of repeated dermal application of glyphosate technical at 5,000 mg/kg/application; no dermal effects were seen at doses ≤1,000 mg/kg/application (EPA 1992c). According to EPA (1993, 2009a), glyphosate is considered a slight dermal irritant following acute dermal application.

2.12 OCULAR

In a study of wives of commercial pesticide applicators, no association was found between glyphosate use among the wives and retinal degeneration (Kirrane et al. 2005); see Table 2-4 for details. In a case series report of 1,513 ocular exposures to glyphosate, minor symptoms (primarily transient irritation) were

observed in 70% of the cases; most (99%) complained of eye pain (Acquavella et al. 1999). Moderate effects, such as persistent irritation or low-grade corneal burns or abrasions, were observed in about 2% of the cases. Among the cases with moderate effects, 93% reported eye pain, 20% reported lacrimation, and 27% reported blurred vision.

Two chronic-duration oral studies included ophthalmoscopic examinations of laboratory animals exposed to glyphosate technical. EPA (1991a, 1991b) reported significantly increased incidence of lens abnormalities in male rats treated via the diet for 2 years at an estimated dose of 940 mg/kg/day; there were no indications of a treatment-related ocular effect in female rats at the highest estimated dose level (1,183 mg/kg/day). No signs of treatment-related ocular effects were seen among dogs treated via capsule for 1 year at estimated doses as high as 500 mg/kg/day (EPA 1986a). According to EPA (1993, 2009a), glyphosate is considered mildly irritating to the eye following ocular instillation.

2.13 ENDOCRINE

Available human information regarding possible associations between exposure to glyphosate-containing products and risk of endocrinological effects is limited to results from one study that reported no associations between any glyphosate exposure and the risks of thyroid diseases (Table 2-4) in the female spouses of Agricultural Health Study participants (Goldner et al. 2010).

Chronic-duration oral studies in rats, mice, and dogs revealed no evidence of glyphosate technical treatment-related effects on the endocrine system (EPA 1985a, 1986a, 1991a, 1992d). Romano et al. (2010) reported dose-related 30–50% decreased serum testosterone in young male rats gavaged with a glyphosate formulation at 5–250 mg/kg/day during postpartum days 23–53. Romano et al. (2012) implicated disruption of gonadotropin expression as a mechanism of action for glyphosate-induced effects on male rat sexual development.

Glyphosate (purity not specified) did not affect testosterone or estradiol levels in an Organisation for Economic Cooperation and Development (OECD) guideline steroidogenesis assay that employed H295R human adrenocortical carcinoma cells (EPA 2012a). A uterotrophic assay employed daily gavage administration of glyphosate (85.1% active ingredient) in 0.5% methylcellulose to sexually-mature ovariectomized Sprague-Dawley rats at 0, 100, 300, or 1,000 mg/kg/day for 3 consecutive days; positive controls received 17α-ethynyl estradiol (EPA 2012b). Glyphosate did not induce an estrogenic response under the conditions of the assay. Glyphosate (95.93% glyphosate acid; calculated glyphosate content of

85.14%) was incubated with human recombinant aromatase and tritiated androstenedione to assess the potential for glyphosate to inhibit aromatase activity *in vitro* (EPA 2012c). Glyphosate did not inhibit aromatase activity under the conditions of the assay.

EPA (2015b) subjected glyphosate to the Endocrine Screening Program Tier 1 and concluded that there was no convincing evidence of potential interaction between glyphosate and estrogen, androgen, or thyroid pathways.

2.14 IMMUNOLOGICAL

Studies examining possible associations between glyphosate exposure and asthma risk or rheumatoid arthritis risk are discussed in Sections 2.4 and 2.8, respectively.

Limited information is available regarding immunological effects. There was no evidence of treatment-related effects on spleen or thymus of mice administered glyphosate technical in the diet for 28 days at estimated doses as high as 1,447.5 mg/kg/day and no evidence of treatment-related effects on splenic anti-sheep red blood cell (SRBC) anti-body forming cell (AFC) responses to SRBC (EPA 2013b). Tizhe et al. (2014) reported histopathologic lesions in the spleen of rats gavaged with a glyphosate formulation at 375 mg/kg/day for 8 weeks. However, the study report did not contain quantitative incidence data, thus precluding independent evaluation. EPA (1992d) reported significantly increased incidences of lymphocytic hyperplasia in the thymus from female rats administered glyphosate technical in the diet for up to 26 months at doses of 3.37, 11.22 and 34.02 mg/kg/day (13/32, 18/37, and 17/34, respectively, versus 5/25 controls). However, EPA (1992d) did not consider the lesion to be compound-related because the lesion occurs spontaneously in older rats and is quite variable in the thymus, there was no apparent effect on lymphocytes in the spleen (a much less variable indicator for lymphocytic hyperplasia), and the severity of the lesion was similar among controls and glyphosate-treated groups.

2.15 NEUROLOGICAL

Available information regarding possible associations between exposure to glyphosate-containing products and risk of neurological effects is limited to a single case-control study that did not find an association between glyphosate exposure and Parkinson's disease (see Table 2-4 for details) (Kamel et al. 2007).

Rats were administered glyphosate technical once by gavage at up to 2,000 mg/kg and observed for up to 2 weeks postdosing; other rats were treated via the diet for 13 weeks at doses as high as 1,547–1,631 mg/kg/day (EPA 2013c). There was no evidence of treatment-related neurotoxicity as assessed by clinical signs, functional observational battery, motor activity testing, and gross and histopathologic examination of brain and peripheral nervous tissue. Tizhe et al. (2014) reported neuronal degeneration in the brain of rats gavaged with a glyphosate formulation at 375 mg/kg/day for 8 weeks. However, the study report did not contain quantitative incidence data, thus precluding independent evaluation.

2.16 REPRODUCTIVE

No association between glyphosate use and fecundability was found among women living at farms in which pesticides were used and were involved in pesticide activities (Curtis et al. 1999). This study also reported an association with improved fecundability when the women were not involved in pesticide activities; see Table 2-4 for additional information.

There was no evidence of treatment-related reproductive effects among parental male or female rats administered glyphosate technical in the diet for 2 generations at estimated doses as high as 1,234–3,134 mg/kg/day (EPA 1992a, 2013a). See Section 2.17 for information regarding treatment-related effects on the reproductive system of male rats exposed to glyphosate formulations during *in utero* and/or postnatal development.

2.17 DEVELOPMENTAL

Several epidemiology studies have examined possible associations between glyphosate use and developmental toxicity; these studies are summarized in Table 2-4. Given that only one study examined each endpoint and the lack of quantification of glyphosate exposure, these results were not considered sufficient for drawing conclusions on the risk of developmental toxicity associated with glyphosate exposure in humans. The studies found associations between maternal preconception exposure to glyphosate and increased risk of spontaneous abortion (Arbuckle et al. 2001) and glyphosate exposure and parent-reported attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD) (Garry et al. 2002). No associations were found between paternal exposure and miscarriages (Savitz et al. 1997), preterm delivery (Savitz et al. 1997), small for gestational age risk (Savitz et al. 1997), or congenital malformations (Garcia et al. 1998). Similarly, no associations were found between maternal glyphosate exposure and birth weight (Sathyanarayana et al. 2010) or neural tube deficits (Rull et al. 2006).

A limited number of studies evaluated developmental endpoints in laboratory animals orally exposed to glyphosate technical; the data are not sufficient to draw conclusions regarding glyphosate-induced developmental effects. Depressed weight and increased incidence of unossified sternebrae were observed in fetuses from rat dams treated by gavage at 3,500 mg/kg/day during GDs 6–19 (EPA 1992e). Increased incidence of kidney tubular dilation was reported for F3b weanlings in a 3-generation study of glyphosate technical (98.7% purity) administered to male and female Sprague-Dawley rats in the diet at an estimated dose level of 30 mg/kg/day; the reported NOAEL was 10 mg/kg/day (EPA 1992g). However, EPA (2009a) considered the increased incidence of kidney tubular dilation in the F3b male weanlings to be a spurious result because there were no signs of treatment-related effects on kidneys of rat offspring in a subsequent 2-generation study at dose levels up to 3,134 mg/kg/day (EPA 1992a). In the 2-generation study, the highest dose level (3,134 mg/kg/day) resulted in up to 14–20% depressed pup body weight and/or body weight gain during the lactation period (EPA 1992a). In another 2-generation oral rat study, exposure via the diet at an estimated dose level of 1,234 mg/kg/day resulted in delayed preputial separation in male pups (EPA 2013a). There were no apparent treatment-related developmental effects in a study of rabbits treated by gavage at up to 350 mg/kg/day during GDs 6–27 (EPA 1992f).

Developmental endpoints were evaluated in three studies that employed oral exposure to glyphosate formulations. The specific role of glyphosate in the reported results is uncertain. Dallegrave et al. (2003) observed an increased incidence of skeletal malformations in fetuses from rat dams gavaged at 500 mg/kg/day during GDs 6–15. Dallegrave et al. (2007) reported decreased sperm production and histopathologic testicular lesions in offspring of rat dams gavaged at 50 mg/kg/day during gestation and lactation. Romano et al. (2010) reported decreased epithelial thickness and increased luminal diameter in seminiferous tubules of male rat pups treated by gavage at 5 mg/kg/day on postpartum days 23–53 and delayed preputial separation at a dose level of 50 mg/kg/day.

2.18 OTHER NONCANCER

No associations were found between glyphosate exposure and increased risks of diabetes (Montgomery et al. 2008) or gestational diabetes (Saldana et al. 2007) in epidemiology studies (see Table 2-4). Metabolic acidosis (Kim et al. 2014; Lee et al. 2008; Moon and Chun 2010; Tominack et al. 1991), hyperkalemia (Kim et al. 2014; Lee et al. 2008; Moon and Chun 2010), and acute pancreatitis (Kim et al. 2014; Moon and Chun 2010) have been reported in case series of individuals ingesting glyphosate; metabolic acidosis was typically reported in >35% of the cases.

2.19 CANCER

A number of case-control and cohort epidemiology studies have examined possible associations between glyphosate exposure and increased cancer risks. These epidemiology studies are summarized in Table 2-5. The majority of the studies used self-reported (or proxy reported) ever/never glyphosate use as the biomarker of exposure and some studies have included a metric for frequency of exposure. The results of these studies should be interpreted cautiously given the lack of monitoring data to quantify glyphosate exposure and the likely exposure to other pesticides. In studies of Agricultural Health Study participants, no associations between glyphosate use and the risk of all cancers (De Roos et al. 2005a) or childhood cancers (Flower et al. 2004) were found. Studies examining the risks of solid tumors have not found associations for cancers of the lung (De Roos et al. 2005a), oral cavity (De Roos et al. 2005a), stomach (Lee et al. 2004b), esophagus (Lee et al. 2004b), colon and/or rectum (De Roos et al. 2005a; Lee et al. 2007), pancreas (Andreotti et al. 2009; De Roos et al. 2005a), kidney (De Roos et al. 2005a), bladder (De Roos et al. 2005a), prostate (Band et al. 2011; De Roos et al. 2005a; Koutros et al. 2013), or breast (Engel et al. 2005). Similarly, no associations were found between glyphosate exposure and melanoma (De Roos et al. 2005a), glioma (Lee et al. 2005; Yiin et al. 2012), or soft tissue sarcoma (Pahwa et al. 2011).

Numerous studies have focused on the risks of lymphohematopoietic cancers. No associations were found between glyphosate exposure and the risks of all lymphohematopoietic cancers (De Roos et al. 2005a), leukemia (Brown et al. 1990; De Roos et al. 2005a), hairy cell leukemia (Nordstrom et al. 1998), multiple myeloma (Brown et al. 1993; De Roos et al. 2005a; Kachuri et al. 2013; Orsi et al. 2009; Pahwa et al. 2012; Sorahan 2015), specific lymphoma types (Cocco et al. 2013; Eriksson et al. 2008), or Hodgkin lymphoma (Karunanayake et al. 2012; Orsi et al. 2009). Mixed results have been reported for non-Hodgkin's lymphoma risk. Increased risk ratios were reported in some studies (De Roos et al. 2003; Eriksson et al. 2008; Hardell et al. 2002); other studies have not found associations (De Roos et al. 2005a; Lee et al. 2004a; McDuffie et al. 2001; Orsi et al. 2009). It is noted that when exposure to other pesticides was considered in the statistical analyses, associations between glyphosate and non-Hodgkin's lymphoma risk were no longer found in the De Roos et al. (2003), Eriksson et al. (2008), and Hardell et al. (2002) studies.

Table 2-5. Cancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
Solid Tumors		
Andreotti et al. 2009 Case-control study of 93 cases of pancreatic cancer (64 applicators and 29 spouses) and 82,503 controls (52,721 applicators and 29,782 spouses) who participated in in Iowa and North Carolina (Agricultural Health Study); 55 cases and 35 controls used for glyphosate analysis	**Exposure:** any glyphosate exposure **Unconditional logistic regression adjustments:** age group, cigarette smoking, diabetes, applicator type	Pancreatic cancer OR 1.1 (0.6–1.7)
Band et al. 2011 Case controls study of 1,516 prostate cancer cases and 4,994 controls in Canada; 25 cases and 60 controls used for glyphosate analysis	**Exposure:** any glyphosate exposure **Conditional logistic regression adjustments:** alcohol consumption, smoking, education, proxy respondent	Prostate cancer OR 1.36 (0.83–2.25)
De Roos et al. 2005a Cohort study of 54,315 licensed pesticide applicators in Iowa and North Carolina (Agricultural Health Study)	**Exposure:** any glyphosate exposure; subjects also grouped by cumulative exposure days of 1–20 days (used as referent group), 21–56 days, and 57–2,678 days **Poisson regression adjustments:** age, smoking, other pesticides (colon, pancreas, kidney, bladder cancers), alcohol consumption, family history of cancer, education (subjects were excluded if covariate data were missing)	All cancers Ever use: RR 1.0 (0.9–1.2) 21–56 days: RR 1.0 (0.9–1.1) 57–2,678 days: RR 1.0 (0.9–1.1) Lung Ever use: RR 0.9 (0.6–1.3) 21–56 days: RR 0.9 (0.5–1.5) 57–2,678 days: RR 0.7 (0.4–1.2) Oral cavity Ever use: RR 1.0 (0.5–1.8) 21–56 days: RR 0.8 (0.4–1.7) 57–2,678 days: RR 0.8 (0.4–1.7) Colon Ever use: RR 1.4 (0.8–2.2) 21–56 days: RR 1.4 (0.9–2.4) 57–2,678 days: RR 0.9 (0.4–1.7) Rectum Ever use: RR 1.3 (0.7–2.3) 21–56 days: RR1.3 (0.7–2.5) 57–2,678 days: RR 1.1 (0.6–2.3)

Table 2-5. Cancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
		Pancreas Ever use: RR 0.7 (0.3–2.0) 21–56 days: RR 1.6 (0.6–4.1) 57–2,678 days: RR 1.3 (0.5–3.6) Kidney Ever use: RR 1.6 (0.7–3.8) 21–56 days: RR 0.6 (0.3–1.4) 57–2,678 days: RR 0.7 (0.3–1.6) Bladder Ever use: R 1.5 (0.7–3.2) 21–56 days: RR 1.0 (0.5–1.9) 57–2,678 days: RR 1.2 (0.6–2.2) Prostate Ever use: RR 1.1 (0.9–1.3) 21–56 days: RR 0.9 (0.7–1.1) 57–2,678 days: RR 1.1 (0.9–1.3) Melanoma Ever use: RR 1.6 (0.8–3.0) 21–56 days: RR 1.2 (0.7–2.3) 57–2,678 days: RR 0.9 (0.5–1.8)
Engel et al. 2005 Prospective study of 30,454 wives of farmers participating in the Agricultural Health Study in Iowa and North Carolina; 82 cases and 10,016 controls for glyphosate all wives analysis and 109 cases and 9,304 controls for wives never using pesticides analysis	**Exposure:** any glyphosate exposure **Poisson regression adjustments:** age, race, state of residence	Breast cancer RR 0.9 (0.7–1.1) for all wives in cohort RR 1.3 (0.8–1.9) among wives who never used pesticides
Flower et al. 2004 Prospective study of 17,357 children whose parents were participants in the Agricultural Health Study in Iowa; 3,321 exposed to glyphosate and 6 cases of childhood cancer	**Exposure:** any glyphosate exposure **Logistic regression adjustments:** child's age at enrollment, race, state of residence	Childhood cancer OR 0.61 (032–1.16), maternal use OR 0.84 (0.35–2.34), paternal use (prenatal)

Table 2-5. Cancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
Koutros et al. 2013 Nested case-control study of 54,412 pesticide applicators (1,962 cases of prostate cancer) in Iowa and North Carolina (Agricultural Health Study); 1,464 cases and 42,420 controls used for glyphosate analysis This contains some subjects examined by Alavanja et al. (2003)	**Exposure:** any glyphosate exposure; subjects also grouped into 4 quartiles of cumulative exposure days **Poisson regression adjustments:** age, state, race, family history of prostate cancer, smoking, fruit servings, leisure-time physical activity in winter	Total prostate cancer Q1: RR 0.91 (0.79–1.06) Q2: RR 0.96 (0.83–1.12) Q3: RR 1.01 (0.87–1.17) Q4: RR 0.99 (0.86–1.15) Aggressive prostate cancer Q1: RR 0.93 (0.74–1.16) Q2: RR 0.91 (0.73–1.13) Q3: RR 1.01 (0.82–1.25) Q4: RR 0.94 (0.75–1.18)
Lee et al. 2004b Case control study of cases of stomach (n=170) or esophagus (n=137) adenocarcinoma and 502 controls in Nebraska; 12 cases of stomach cancer, 12 cases of esophageal cancer, and 46 controls were used for glyphosate analysis	**Exposure:** any glyphosate exposure **Unconditional logistic regression adjustments:** age, sex	Stomach cancer OR 0.8 (0.4–1.5) Esophageal cancer OR 0.7 (0.3–1.4)
Lee et al. 2005 Case control study of 251 cases of gliomas and 498 controls in Nebraska; 17 cases and 32 controls (overall) for glyphosate analysis	**Exposure:** any glyphosate exposure **Unconditional logistic regression adjustments:** age, sex, respondent type	Glioma OR 1.5 (0.7–3.1), all subjects OR 0.4 (0.1–1.6), self-reported glyphosate use OR 3.1 (1.2–8.2), proxy-reported glyphosate use
Lee et al. 2007 Prospective cohort study of 56,813 pesticide applicators in Iowa and North Carolina (Agricultural Health Study); 225 cases and 67 controls, 151 cases and 49 controls, and 74 cases and 18 controls for colorectal, colon, and rectal cancers, respectively, for glyphosate analysis	**Exposure:** any glyphosate exposure **Unconditional logistic regression adjustments:** age, state of residence, smoking history, total pesticide application days to any pesticide	Colorectal cancer OR 1.2 (0.9–1.6) Colon cancer OR 1.0 (0.7–1.5) Rectal cancer OR 1.6 (0.9–2.9)

Table 2-5. Cancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
Pahwa et al. 2011 Case controls study of 357 soft tissue sarcoma cases and 1,506 controls in Canada; 32 cases and 147 controls were used for glyphosate analysis	**Exposure:** any glyphosate exposure **Conditional logistic regression adjustments:** age, province of residence, medical history	Soft tissue sarcoma OR 0.90 (0.58–1.40)
Yiin et al. 2012 Case control study of 798 cases of glioma and 1,175 controls in Iowa, Michigan, Minnesota, and Wisconsin (Upper Midwest Health Study); 12 cases and 19 controls were used for glyphosate analysis	**Exposure:** Estimated exposure **Unconditional logistic regression adjustments:** age, 10-year age group, sex, education, farm pesticide use	Glioma Non-farm jobs: OR 0.83 (0.39–1.73) Garden pesticide use: OR 0.98 (0.67–1.43) Similar results were found when proxy respondents were excluded
Lymphohematopoietic cancers		
Brown et al. 1990 Case-control study of 243 cases of leukemia in males and 547 controls in Iowa and Minnesota; 15 cases and 49 controls were used for glyphosate analysis	**Exposure:** any glyphosate exposure **Unconditional logistic regression adjustments:** vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, high risk exposures in a logistic analysis	Leukemia OR 0.9 (0.5–1.6)
Brown et al. 1993 Case-control study of 173 cases of multiple myeloma in males and 650 controls in Iowa; 11 cases and 40 controls were used for glyphosate analysis	**Exposure:** any glyphosate exposure **Unconditional logistic regression adjustments:** vital status, age	Multiple myeloma OR 1.7 (0.8–3.8)
Cocco et al. 2013 Case control study of 2,348 cases of B-cell lymphoma and 2,462 controls in Czech Republic, France, Germany, Italy, Ireland, and Spain; 4 cases and 2 controls were used for glyphosate analysis	**Exposure:** any glyphosate exposure **Unconditional logistic regression adjustments:** age, sex, education, center	B-cell lymphoma: OR 3.1 (0.6–17.1)

Table 2-5. Cancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
De Roos et al. 2003 Case control study of 650 cases of non-Hodgkin's lymphoma in adult males and 1,933 male controls in Nebraska, Iowa, Minnesota, and Kansas; 36 cases and 61 controls were used for glyphosate analysis This contains pooled data from Cantor et al. (1992), Hoar et al. (1986), Lee et al. (2004a), and Zahm et al. (1990) studies	**Exposure:** any glyphosate exposure **Logistic regression and hierarchical regression model adjustments:** age, study site, and use of all other pesticides	Non-Hodgkin's lymphoma OR 2.1 (1.1–4.0) using logistic regression OR 1.6 (0.9–2.8) using hierarchical regression
De Roos et al. 2005a Cohort study of 54,315 licensed pesticide applicators in Iowa and North Carolina (Agricultural Health Study); 190, 32, 57, and 92 cases of all lymphohematopoietic cancers, multiple myeloma, leukemia, and non-Hodgkin's lymphoma were used in glyphosate analyses	**Exposure:** any glyphosate exposure; subjects also grouped by cumulative exposure days of 1–20 days (used as referent group), 21–56 days, and 57–2,678 days **Poisson regression adjustments:** age, smoking, other pesticide, alcohol consumption, family history of cancer, education (subjects were excluded if covariate data were missing)	All lymphohematopoietic cancers Ever use: RR 1.1 (0.8–1.6) 21–56 days: RR 1.2 (0.8–1.8) 57–2,678 days: RR 1.2 (0.8–1.8) Multiple myeloma Ever use: RR 2.6 (0.7–9.4) 21–56 days: RR 1.1 (0.4–3.5) 57–2,678 days: RR 1.9 (0.6–6.3) Leukemia Ever use: RR 1.0 (0.5–1.9) 21–56 days: RR 1.9 (0.8–4.5) 57–2,678 days: RR 1.0 (0.4–2.9) Non-Hodgkin's lymphoma Ever use: RR 1.1 (0.7–1.9) 21–56 days: RR 0.7 (0.4–1.4) 57–2,678 days: RR 0.9 (0.5–1.6)
Eriksson et al. 2008 Case control study of 910 cases (adult males and females) of non-Hodgkin's lymphoma and 1,016 controls in Sweden; for glyphosate analyses, 12 cases and 9 controls for <10 days and 17 cases and 9 controls for >10 days used for non-Hodgkin's lymphoma	**Exposure:** any glyphosate exposure **Unconditional logistic regression adjustments:** age, sex, year of diagnosis/enrollment	Non-Hodgkin's lymphoma OR 2.02 (1.10–3.71) OR 1.51 (0.77–2.94) (with adjustment for other pesticides) Exposure of ≤10 days/year OR 1.69 (0.70–4.07) Exposure of >10 days/year OR 2.36 (1.04–5.37)

Table 2-5. Cancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
		B-cell lymphoma OR 1.87 (0.99–3.51) Lymphocytic lymphoma/B-cell lymphoma OR 3.35 (1.42–7.89) Follicular, grade I–III OR 1.89 (0.62–5.79) Diffuse large B-cell lymphoma OR 1.22 (0.44–3.35) Other specified B-cell lymphoma OR 1.63 (0.53–4.96) Unspecified B-cell lymphoma OR 1.47 (0.33–6.61) T-cell lymphomas OR 2.29 (0.51–10.4) Unspecified hairy cell leukemia OR 5.63 (1.44–22.0)
Hardell et al. 2002 Case control study of 515 cases of non-Hodgkin's lymphoma and hairy cell leukemia and 1,141 controls in Sweden; 8 cases and 8 controls used for glyphosate analysis This contains pooled data from Hardell and Eriksson (1999) and Nordström et al. (1998)	**Exposure:** any glyphosate exposure **Multivariate analysis adjustments:** age, study site, vital status, exposure to other pesticides	Non-Hodgkin's lymphoma or hairy cell leukemia OR 3.04 (1.08–8.52) (without adjustment for other pesticides) OR 1.85 (0.55–6.20) (with adjustment for other pesticides)
Kachuri et al. 2013 Case control study of 342 male cases of multiple myeloma and 1,357 controls in Canada; 32 cases and 121 controls used for glyphosate analysis	**Exposure:** any glyphosate exposure **Unconditional logistic regression adjustments:** age, province of residence, use of proxy respondents, smoking, personal and family medical history	Multiple myeloma OR 1.19 (0.76–1.87) OR 0.72 (0.39–1.32), glyphosate use ≤2 times/year OR 2.04 (0.98–4.23), glyphosate use >2 times/year Similar results when proxy responders were excluded from analysis

Table 2-5. Cancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
Karunanayake et al. 2012 Case control study of 316 male cases of Hodgkin lymphoma and 1,506 controls in Canada; 38 cases and 133 controls used for glyphosate analysis	**Exposure:** any glyphosate exposure **Conditional logistic regression adjustments:** age, province of residence, personal and family medical history	Hodgkin lymphoma OR 0.99 (0.62–1.56)
Lee et al. 2004a Case control study of 872 cases of non-Hodgkin's lymphoma and 2,381 controls in Iowa, Minnesota, and Nebraska; for glyphosate analyses, 53 cases and 91 controls for nonasthmatics and 6 cases and 12 controls for asthmatics These data were used in the pooled analysis by De Roos et al. (2003)	**Exposure:** any glyphosate exposure **Unconditional logistic regression adjustments:** age, state, vital status	Non-Hodgkin's lymphoma OR 1.4 (0.98–2.1), nonasthmatics OR 1.2 (0.4–3.3), asthmatics
McDuffie et al. 2001 Case control study of 517 males cases of non-Hodgkin's lymphoma and 1,506 controls in Canada; 51 cases and 133 controls used for glyphosate analyses	**Exposure:** any glyphosate exposure **Conditional logistic regression adjustments:** age, province of residence, medical history (measles, mumps, cancer, allergy desensitization shots, positive family history of cancer in 1st-degree relative	Non-Hodgkin's lymphoma OR 1.20 (0.83–1.74) Exposure >0 and ≤2 days/year OR 1.00 (0.63–1.57) Exposure >2 days/year OR 2.12 (1.20–3.73)
Nordström et al. 1998 Case control study of 111 cases of hairy cell leukemia and 400 controls in Sweden; adult males; hairy cell leukemia is a subtype of Non-Hodgkin's lymphoma; 4 cases and 5 controls were used for glyphosate analysis These data were used in the pooled analysis by De Roos et al. (2003)	**Exposure:** any glyphosate exposure (at least 1 working day **Logistic regression adjustments:** age	Hairy cell leukemia OR 3.1 (0.8–12)

Table 2-5. Cancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
Orsi et al. 2009 Case control study of 491 cases of lymphoid neoplasms (244 cases non-Hodgkin's lymphoma, 87 cases Hodgkin's lymphoma, 104 cases of lymphoproliferative syndromes, 56 cases of multiple myeloma) and 456 controls in France; for glyphosate analyses, the number of cases/controls were 27/24, 12/24, 6/15, 4/18, and 5/18 for lymphoid neoplasms, non-Hodgkin's lymphoma, Hodgkin's lymphoma, lymphoproliferative syndrome, and multiple myeloma, respectively	**Exposure:** any glyphosate exposure **Unconditional logistic regression adjustments:** age, center	Lymphoid neoplasms OR 1.2 (0.6–2.1) Non-Hodgkin's lymphoma OR 1.0 (0.5–2.2), all subtypes OR 1.0 (0.3–2.7) for diffuse large cell lymphoma OR 1.4 (0.4–5.2) for follicular lymphoma Hodgkin's lymphoma OR 1.7 (0.6–5.0) Lymphoproliferative syndrome OR 0.6 (0.2–2.1), all subtypes OR 0.4 (0.1–1.8) for chronic lymphocytic leukemia OR 1.8 (0.3–9.3) for hairy cell leukemia Multiple myeloma OR 2.4 (0.8–7.3)
Pahwa et al. 2012 Case controls study of 342 multiple myeloma cases and 1,506 controls in Canada; 32 cases and 133 controls were used for glyphosate analysis	**Exposure:** any glyphosate exposure **Conditional Logistic regression adjustments:** age, province of residence, medical history	Multiple myeloma OR 1.22 (0.77–1.93)

Table 2-5. Cancer Outcomes in Humans Exposed to Glyphosate

Reference and study population	Exposure	Outcomes
Sorahan 2015 Cohort study of 40,719 licensed pesticide applicators (30,910 glyphosate users) in Iowa and North Carolina (Agricultural Health Study); cohort excluded workers with missing data for other pesticide use; glyphosate analyses based on 19 cases and 3 controls Re-analysis of data reported by De Roos et al. (2005)	**Exposure:** any glyphosate exposure; subjects also grouped by cumulative exposure days of 1–20 days (used as referent group), 21–56 days, and 57–2,678 days and by intensity weighted exposure days of 0.1–79.5, 79.6–337.1 , and 337.2–18,241 **Poisson regression adjustments:** age, smoking, alcohol consumption, family history of cancer, education, level of use of some pesticides (2,4-D, alachlor, atrazine, metolachlor, trifluralin), ever use of other pesticides (maneb, paraquat, carbaryl, diazonon, benomyl)	Multiple myeloma Ever use: RR 2.79 (0.78–9.96) Ever use: RR 2.21 (0.65–7.48), only adjusted for age 57–2,678 days: RR 1.38 (0.42–4.45), p>0.50 for trend 337.2–18,241 units: RR 1.87 (0.67–5.27), p=0.18 for trend

OR = odds ratio; RR = relative risk

1

Several meta-analyses have been conducted for lymphohematopoietic cancers; the results of these analyses are presented in Table 2-6. Schinasi and Leon (2014), IARC (2015, 2016) and Chang and Delzell (2016) conducted independent meta-analyses of non-Hodgkin's lymphoma data from six individual studies (De Roos et al. 2003, 2005a; Eriksson et al. 2008; Hardell et al. 2002; McDuffie et al. 2001; Orsi et al. 2009) and estimated meta risk ratios of 1.5 (95% confidence interval [CI] 1.1–2.0), 1.3 (95% CI 1.03–1.65), and 1.3 (95% CI 1.0–1.6), respectively. Chang and Delzell (2016) performed meta-analyses for non-Hodgkin's lymphoma subtypes (diffuse large B-cell lymphoma, B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic leukemia, hairy-cell leukemia), as well as other types of lymphohematopoietic cancers (leukemia, multiple myeloma, and Hodgkin's lymphoma). A significant association was found for B-cell lymphoma (meta risk ratio 2.0; 95% CI 1.1–3.6) based on two studies; no significant associations were found for the other tumor types.

Table 2-6. Summary of Meta-Analyses of Results from Studies Examining Possible Association Between Self-Reported Use of Glyphosate and Lymphohematopoietic Cancers

Outcome	Studies included in analysis	Meta-analysis risk	Reference
Non-Hodgkin's lymphoma	De Roos et al. 2003 De Roos 2005a Eriksson et al. 2008 Hardell et al. 2002 McDuffie et al. 2001 Orsi et al. 2009	RR 1.5 (95% CI 1.1–2.0) I^2 = 32.7%	Schinasi and Leon 2014
Non-Hodgkin's lymphoma	De Roos et al. 2003 De Roos 2005a Eriksson et al. 2008 Hardell et al. 2002 McDuffie et al. 2001 Orsi et al. 2009	RR 1.3 (95% CI 1.03–1.65) I^2 = 0.0%, p=0.84 for heterogeneity	IARC 2015, 2016
Non-Hodgkin's lymphoma	De Roos et al. 2003 De Roos 2005a Eriksson et al. 2008 Hardell et al. 2002 McDuffie et al. 2001 Orsi et al. 2009	RR 1.3 (95% CI 1.0–1.6) I^2 = 0.0%, p=0.84 for heterogeneity	Chang and Delzell 2016
B-cell lymphoma	Cocco et al. 2013 Eriksson et al. 2008	RR 2.0 (95% CI 1.1–3.6) I^2 = 0.0%, p=0.58 for heterogeneity	Chang and Delzell 2016
Leukemia	Brown et al. 1990 De Roos et al. 2005a Kaufman et al. 2009	RR 1.0 (95% CI 0.6–1.5) I^2 = 0.0%[a], p=0.92 for heterogeneity	Chang and Delzell 2016
Multiple myeloma	Brown et al. 1993 Kachuri et al. 2013 Orsi et al. 2009 Sorahan 2015	RR 1.4 (95% CI 1.0–1.9) I^2 = 0.0%, p=0.63 for heterogeneity	Chang and Delzell 2016

Table 2-6. Summary of Meta-Analyses of Results from Studies Examining Possible Association Between Self-Reported Use of Glyphosate and Lymphohematopoietic Cancers

Outcome	Studies included in analysis	Meta-analysis risk	Reference
Hodgkin's lymphoma	Karunanayake et al. 2012 Orsi et al. 2009	RR 1.1 (95% CI 0.7–1.6) I^2 = 0.0%, p=0.36 for heterogeneity	Chang and Delzell 2016

[a]I^2 is a measure of total variance explained by study heterogeneity and measure of inconsistency in results; higher values indicate greater inconsistency.

CI = confidence interval; RR = risk ratio

EPA evaluated results from two unpublished rat studies in which the carcinogenicity of glyphosate technical was assessed and summarized the findings in publicly-available DERs (EPA 1991a, 1991b, 1992d).

Groups of weanling Sprague-Dawley rats (50/sex/group) were administered glyphosate technical (98.7% purity) in the diet for up to 26 months at initial concentrations of 0, 30, 100, or 300 ppm (EPA 1992d). Based on body weight and food consumption data, concentrations of glyphosate technical were adjusted to achieve oral doses of 0, 3.05, 10.30, and 31.49 mg/kg/day, respectively, for males and 0, 3.37, 11.22, and 34.02 mg/kg/day, respectively, for females. Incidences of testicular interstitial cell tumors in the control, low-, mid-, and high-dose male rats were 0/50 (0%), 3/50 (6%), 1/50 (2%), and 6/50 (12%), respectively (Table 2-7). The incidence in the high-dose males was statistically significant (p=0.013) in pairwise comparison to the control incidence. Evaluation of historical control incidences resulted in testicular interstitial cell tumor incidences in the range of 0–12%, with a mean incidence of 4.5% (range: 3.4–6.7%) among lifetime studies that employed the same rat strain and were conducted concurrently with the 26-month study. EPA (1992d) concluded that the incidences were within the normal variation for this tumor type in the Sprague-Dawley rat strain. EPA (2016a) applied a weight-of-evidence approach to evaluation of the testicular interstitial cell tumor incidence data. EPA (2016a) noted a lack of evidence of a monotonic dose response due to greater incidence in the low-dose group compared to the mid-dose group (although a significant trend [p=0.009] for the testicular interstitial cell tumors was observed), a lack of testicular interstitial cell tumors (0% incidence) in the control group compared to historical control incidences in the range of 3.4–6.7% (in which case, the 0% incidence in the control group may have created an artificial statistically significant increased incidence in the high-dose group), and an absence of preneoplastic or related nonneoplastic lesions. Based on the weight-of-evidence, EPA (2016a) did not consider the increases in testicular interstitial cell tumors to be treatment-related.

Table 2-7. Incidences of Selected Tumors in Sprague-Dawley Rats Administered Technical Glyphosate (98.7% purity) in the Diet for up to 26 Months

	Glyphosate dose (mg/kg/day)				Historical control incidence
	0	3.05	10.3	31.49	
Male rats					
Testes interstitial cell tumors					
Interstitial cell tumors	0/50 (0%)	3/50 (6%)	1/50 (8%)	6/50[a] (12%)	3.4–6.7%
Female rats					
Thyroid c-cell tumors					
Adenoma	5/47 (11%)	3/49 (6%)	6/50 (14%)	3/47 (6%)	0–17%
Carcinoma	1/47 (2%)	0/49 (0%)	2/50 (4%)	6/47 (13%)	0–5%
Adenoma or carcinoma (combined)	6/47 (13%)	3/49 (6%)	8/50 (16%)	9/47 (19%)	0–17%

[a]Significantly different from concurrent control according to Fisher's Exact Test ($p<0.05$).

NA = not applicable; NS = not specified

Sources: EPA 1992d, 2016a

Incidences of thyroid c-cell tumors (adenoma, carcinoma, combined adenoma or carcinoma) in the female rats are presented in Table 2-7. Incidences of thyroid c-cell carcinomas in female rats were borderline significantly ($p=0.055$) increased at the highest dose (6/47 versus 1/47 for controls) (EPA 1992d). However, the incidence of combined c-cell carcinomas or adenomas was not significantly increased (9/47 high-dose females versus 6/47 controls). Furthermore, time-to-tumor analysis revealed no sign of a treatment-related effect. Historical control incidences of spontaneous thyroid c-cell tumors in female Sprague-Dawley rats were as high as 17%. EPA (1992d) concluded that the thyroid c-cell carcinomas in the high-dose female rats were not compound-related.

In the other rat study, groups of albino Sprague-Dawley rats (60/sex/group) were administered technical glyphosate (96.5% purity) in the diet at target concentrations of 0, 2,000, 8,000, or 20,000 ppm (mean measured concentrations of 0, 1,900, 7,600, and 19,000 ppm, respectively) for up to 24 months (EPA 1991a, 1991b). Based on mean body weight and food consumption data, estimated glyphosate doses to controls and low-, mid-, and high-dose groups were 0, 89, 362, and 940 mg/kg/day, respectively, for the males and 0, 113, 457, and 1,183 mg/kg/day, respectively, for the females. As shown in Table 2-8, low-dose (but not mid- or high-dose) males exhibited significantly increased incidences of pancreatic islet cell adenoma ($p=0.015$) in pairwise comparison to control incidence (EPA 1991a, 1991b). Incidences of pancreatic islet cell carcinoma in low-, mid-, and high-dose males were not significantly different from control incidences. Incidences of combined adenoma or carcinoma among mid-, and high-dose males

were not significantly different from control incidences. After excluding those male rats that died or were sacrificed prior to treatment week 55 (before the first adenoma or carcinoma were observed), incidences of pancreatic islet cell adenoma in the low--dose group remained significantly (p=0.018) higher than controls. However, exclusion of the early deaths resulted in only borderline significantly increased incidence of combined adenoma or carcinoma (p=0.052) in the low-dose group. Historical control incidences for pancreatic islet cell adenoma in male rats from 2-year studies conducted at the same testing facility ranged from 1.8 to 8.5% (mean 5.3%). In the female rats, no significant differences were observed between controls and treated rats regarding pancreatic islet cell tumor incidences in pairwise comparisons with controls. EPA (2016a) applied a weight-of-evidence approach to analysis of evaluation of the pancreatic islet cell tumor incidence data for the male rats. EPA (2016a) noted that significant differences in pairwise comparisons between controls and low- and high-dose males may have resulted from unusually low incidence in the concurrent control group rather than from glyphosate treatment, that none of the incidences achieved statistical significance after excluding rats that died prior to treatment week 55 and adjusting for multiple comparisons, that pancreatic islet cell carcinoma was observed only in the control group, and that there was a lack of supporting preneoplastic or nonneoplastic changes indicative of a progression from adenoma to carcinoma. Based on the weight of evidence, EPA (2016a) did not consider the increases in pancreatic islet cell tumors in the male rats to be treatment-related.

Table 2-8. Incidences of Selected Tumors in Albino Sprague-Dawley Rats Administered Technical Glyphosate (96.5% Purity) in the Diet for 2 Years

	Glyphosate dose (mg/kg/day)				Historical control incidence
	0	89	362	940	
Male rats					
Pancreatic islet cell tumors					
All deaths considered					
Adenoma	1/58 (2%)	8/57[a] (14%)	5/60 (8%)	7/59 (12%)	1.8–8.5%
Carcinoma	1/58 (2%)	0/57 (0%)	0/60 (0%)	0/59 (0%)	NS
Adenoma or carcinoma (combined)	2/58 (3%)	8/57 (14%)	5/60 (8%)	7/59 (12%)	NA
Excluding deaths prior to treatment week 55 (first adenoma at week 81; first carcinoma at week 105)					
Adenoma	1/43 (2%)	8/45[a] (18%)	5/49 (8%)	7/48 (15%)	NA
Carcinoma	1/43 (2%)	0/45 (0%)	0/49 (0%)	0/48 (0%)	NA
Adenoma or carcinoma (combined)	2/43 (2%)	8/45 (18%)	5/49 (10%)	7/48 (15%)	NA

Table 2-8. Incidences of Selected Tumors in Albino Sprague-Dawley Rats Administered Technical Glyphosate (96.5% Purity) in the Diet for 2 Years

	Glyphosate dose (mg/kg/day)				Historical control incidence
	0	89	362	940	
Thyroid c-cell tumors					
All deaths considered					
Adenoma	2/60 (3%)	4/58 (7%)	8/58[b] (14%)	7/60 (12%)	1.8–10.6%
Carcinoma	0/60 (0%)	2/58 (3%)	0/58 (0%)	1/60 (2%)	NS
Excluding deaths prior to treatment week 55 (first adenoma at week 54; first carcinoma at week 93)					
Adenoma	2/54 (4%)	4/55 (7%)	8/58 (14%)	7/58 (12%)	NA
Carcinoma	0/54 (0%)	2/55 (4%)	0/58 (0%)	1/58 (1%)	NA
Adenoma or carcinoma (combined)	2/54 (4%)	6/55 (11%)	8/58 (14%)	8/48 (14%)	NA
Female rats					
Pancreatic islet cell tumors					
All deaths considered					
Adenoma	5/60 (8%)	1/60 (2%)	4/60 (7%)	0/59 (0%)	NS
Carcinoma	0/60 (0%)	0/60 (0%)	0/60 (0%)	0/59 (0%)	NS
Adenoma or carcinoma (combined)	5/60 (8%)	1/60 (2%)	4/60 (7%)	0/59 (0%)	NA
Thyroid c-cell tumors					
All deaths considered					
Adenoma	2/60 (3%)	2/60 (3%)	6/60 (10%)	7/60 (10%)	3.3–10%
Carcinoma	0/60 (0%)	0/60 (0%)	1/60 (2%)	0/60 (0%)	0–2.9%

[a]Significantly different from concurrent control according to Fisher's Exact Test ($p<0.05$).
[b]Marginally significantly different from concurrent control according to Fisher's Exact Test ($p=0.051$).

NA = not applicable; NS = not specified

Sources: EPA 1991a, 1991b, 2016a

As shown in Table 2-8, the incidence of thyroid c-cell adenoma in mid-dose (but not low- or high-dose) male rats was marginally significantly ($p=0.051$) greater than that of controls. Historical control incidences for thyroid c-cell adenoma in male rats ranged from 1.8 to 10.6%. Pairwise comparison with concurrent controls revealed no significant difference between controls and low-, mid-, or high-dose groups regarding incidences of thyroid c-cell adenoma or carcinoma. There were no significant differences between controls and low-, mid-, or high-dose groups regarding incidences of thyroid c-cell adenoma after excluding those male rats that died or were sacrificed prior to week 55 (EPA 2016a). In the female rats, no significant differences were observed between controls and treated rats regarding thyroid c-cell tumor incidences in pairwise comparisons with controls. In a weight-of-evidence approach

to evaluation of thyroid c-cell tumors, EPA (2016a) noted a lack of statistically significant incidences or trends for thyroid c-cell tumors in glyphosate-treated male rats after excluding those rats that died prior to treatment week 55, marginally statistically significant trends for adenomas (p=0.040) and adenomas or carcinomas combined (p=0.042) in female rats in the absence of statistical significance in pairwise analyses, a lack of monotonic dose-response for incidences and severity of thyroid c-cell hyperplasia, and a lack of evidence for progression from adenoma to carcinoma. Based on the weight of evidence, EPA (2016a) did not consider the increases in thyroid tumors to be treatment-related.

EPA evaluated a 2-year mouse dietary study that assessed the potential carcinogenicity of glyphosate technical (EPA 1985a, 1985b, 1986b, 1993, 2015a, 2016a). The following summary is based on ATSDR's evaluation of cancer endpoints summarized in the most recent publicly-available EPA summaries (EPA 2015a, 2016a).

Groups of CD-1 mice (50/sex/group) were administered technical glyphosate (99.78% purity) for 24 months at doses of 0, 161, 835, or 4,945 mg/kg/day to the males and 0, 195, 968, or 6,069 mg/kg/day to the females (EPA 1985a, 1985b, 1986b, 1989, 1993, 2015a, 2016a). Guidelines for testing of chemicals for carcinogenicity generally consider 1,000 mg/kg/day as an upper limit for oral dosing (e.g., OECD Test Guideline 451, available at: http://www.oecd.org/chemicalsafety/testing/41753121.pdf). The highest dose tested in the mouse study far exceeds the upper limit and the mid-dose level approached the upper limit. There were no treatment-related effects on tumor incidences in the female mice. Table 2-9 shows incidence data for renal tubule tumors in the male mice summarized by EPA (2016a). There were no statistically significant trends for increased incidence of renal tubule adenoma, carcinoma, or combined carcinoma or adenoma and no statistically significant differences between groups upon pairwise analyses. Although renal tubule adenoma is considered rare in male CD-1 mice, EPA (2016a) noted that a pathology working group (PWG) requested by the Agency evaluated the kidney sections from the male mice and unanimously concluded that the renal tubule tumors were not glyphosate-related due to a lack of statistical significance in pairwise and trend analyses, lack of multiple renal tumors in any of the mice, and lack of compound-related nephrotoxic lesions (including preneoplastic changes). The PWG noted that renal tubular cell tumors are spontaneous lesions for which adequate historical control data are lacking for male CD-1 mice. Based on a weight-of-evidence approach, EPA (2016a) concurred with the PWG conclusions that the renal tubular neoplasms in the male CD-1 mice were not treatment-related.

Table 2-9. Incidences of Renal Tubular Cell Tumors in Male CD-1 Mice Administered Technical Glyphosate (99.78% Purity) in the Diet for up to 24 Months

	Dose (mg/kg/day)			
	0	161	835	4,945
Adenoma	1/49 (2%)	0/49 (0%)	0/50 (0%)	1/50 (2%)
Carcinoma	0/49 (0%)	0/49 (0%)	1/50 (2%)	2/50 (4%)
Adenoma or carcinoma (combined)	1/49 (2%)	0/49 (0%)	1/50 (2%)	3/50 (6%)

Source: EPA 2015a, 2016a

Other unpublished animal carcinogenicity studies were evaluated by the International Agency for Research on Cancer (IARC 2015, 2016), EPA (2016a, 2016b), and other agencies or organizations (e.g., APVMA 2017; EFSA 2015; IPCS 1994; NZ EPA 2016; FAO and WHO 2016). These studies have not been made available to ATSDR for independent review and are therefore not included in this Toxicological Profile for Glyphosate.

IARC (2015, 2016) evaluated available human and animal carcinogenicity assessments, as well as mechanistic and genotoxicity data, and classified glyphosate as Group 2A (*probably carcinogenic to humans*). This classification is based on IARC's conclusions that there is "*limited evidence*" in humans, "*sufficient evidence*" in animals, and evidence that glyphosate and glyphosate-based formulations are genotoxic and capable of inducing oxidative stress.

EPA's Office of Pesticide Programs also reviewed available human and animal carcinogenicity assessments, and genotoxicity data (EPA 2016a) as part of a Registration Review for glyphosate. EPA (2016a) identified 23 epidemiological studies, 15 animal carcinogenicity studies, and nearly 90 genotoxicity studies for glyphosate. EPA (2016a) stated that results from animal carcinogenicity studies and genotoxicity studies consistently demonstrated a lack of clear association between glyphosate exposure and cancer. Regarding human data, EPA (2016a) cited a lack of evidence for an association between exposure to glyphosate and numerous cancer outcomes. However, for assessment of non-Hodgkin's lymphoma, conflicting results and various limitations in the epidemiological studies precluded a definitive conclusion by EPA regarding a possible association between glyphosate exposure and non-Hodgkin's lymphoma (EPA 2016a). Overall, EPA (2016a) concluded that the weight-of-evidence provided the strongest support for a classification of "*not likely to be carcinogenic to humans*" at doses relevant to human health risk assessment. EPA solicited the FIFRA Scientific Advisory Panel (SAP) to consider and review scientific issues associated with the EPA (2016a) evaluation of the carcinogenic

potential of glyphosate. EPA (2017a) includes meeting minutes and the final report from the FIFRA SAP review. Some FIFRA SAP panel members agreed with the EPA (2016a) characterization of glyphosate as "*not likely to be carcinogenic to humans*," whereas other panel members considered the descriptor of "*suggestive evidence of carcinogenic potential*" to be more appropriate. Many panel members noted the equivocal nature of the database and expressed desire for additional data on cancer morbidity and/or mortality from studies of glyphosate-exposed workers.

The European Food Safety Authority evaluated the potential carcinogenicity of glyphosate and concluded that glyphosate was unlikely to pose a carcinogenic hazard to humans (EFSA 2015). The FAO/WHO Joint Meeting on Pesticide Residues concluded that glyphosate was unlikely to pose a carcinogenic risk to humans from dietary exposure (FAO and WHO 2016).

The U.S. Department of Health and Human Services Report on Carcinogens (14th edition) does not include an evaluation of glyphosate (NTP 2016).

2.20 GENOTOXICITY

The potential genotoxicity of glyphosate technical and glyphosate formulations has been extensively evaluated. Results from publicly-available *in vitro* and *in vivo* genotoxicity tests for glyphosate technical are presented in Tables 2-10 and 2-11, respectively. Results from publicly-available *in vitro* and *in vivo* genotoxicity tests for selected glyphosate formulations are presented in Tables 2-12 and 2-13, respectively.

Table 2-10. Genotoxicity of Glyphosate Technical *In Vitro*

Species (test system)	Test substance purity	Endpoint	Result: Activation: With	Result: Activation: Without	Reference
Salmonella typhimurium TA98, TA100, TA1535, TA1537	NS	Gene mutation	–	–	EPA 1992i
S. typhimurium TA98, TA100	NS	Gene mutation	–	–	Kubo et al. 2002
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	98%	Gene mutation	–	–	Li and Long 1988
S. typhimurium TA97, TA98, TA100, TA1535	98.6%	Gene mutation	–	–	NTP 1992

Table 2-10. Genotoxicity of Glyphosate Technical *In Vitro*

Species (test system)	Test substance purity	Endpoint	Result: Activation With	Result: Activation Without	Reference
Escherichia coli WP2 *hcr*	98%	Gene mutation	–	–	Li and Long 1988
Chinese hamster ovary cells	98%	Gene mutation	–	–	Li and Long 1988
Bacillus subtilis rec+, *rec*-	98%	*rec* assay	NT	–	Li and Long 1988
Human peripheral blood lymphocytes	>98%	Chromosomal aberrations	NT	+	Lioi et al. 1998a
Bovine peripheral blood lymphocytes	≥98%	Chromosomal aberrations	NT	+	Lioi et al. 1998b
Human peripheral blood lymphocytes	>96%	Chromosomal aberrations	NT	–	Mañas et al. 2009
Human peripheral blood lymphocytes	>98%	Sister chromatid exchange	NT	(+)	Lioi et al. 1998a
Human peripheral blood peripheral blood	99.9%	Sister chromatid exchange	NT	+	Bolognesi et al. 1997
Bovine peripheral blood lymphocytes	≥98%	Sister chromatid exchange	NT	(+)	Lioi et al. 1998b
Human peripheral blood lymphocytes	98%	Micronuclei	+/–	–	Mladinic et al. 2009a
Human peripheral blood lymphocytes	98%	Micronuclei	+/–	–	Mladinic et al. 2009b
Human-derived buccal epithelial cells	95%	Micronuclei	NT	+	Koller et al. 2012
Chinese hamster CHO-K1 cells	NS	Micronuclei	–	+	Roustan et al. 2014
Rat hepatocytes	98%	Unscheduled DNA synthesis	NT	–	Li and Long 1988
Human fibroblast CM5757 cells	96%	DNA damage	NT	+	Alvarez-Moya et al. 2014
Human peripheral blood lymphocytes	98.4%	DNA damage	NT	+	Lueken et al. 2004
Human peripheral blood lymphocytes	96%	DNA damage	NT	+	Mañas et al. 2009
Human peripheral blood lymphocytes	98%	DNA damage	+	+	Mladinic et al. 2009a

– = negative result; + = positive result; (+) = weakly positive result; +/– = equivocal result; DNA = deoxyribonucleic acid; NS = not specified; NT = not tested

1

Table 2-11. Genotoxicity of Glyphosate Technical *In Vivo*

Species (test system)	Test substance purity	Endpoint	Result	Reference
Rat (bone marrow)	98%	Chromosomal aberrations	–	Li and Long 1988
Mouse (bone marrow)	98.6%	Micronuclei	–	NTP 1992
Mouse (bone marrow)	99.9%	Micronuclei	+	Bolognesi et al. 1997
Mouse (bone marrow)	96%	Micronuclei	+	Mañas et al. 2009
Mouse (bone marrow)	NS[a]	Micronuclei	–	Rank et al. 1993
Mouse (liver DNA)	99.9%	DNA damage	+	Bolognesi et al. 1997
Mouse (kidney DNA)	99.9%	DNA damage	+	Bolognesi et al. 1997
Mouse (liver DNA)	99.9%	Oxidative DNA damage	+	Bolognesi et al. 1997
Mouse (kidney DNA)	99.9%	Oxidative DNA damage	–	Bolognesi et al. 1997
Mouse (liver, kidney DNA)	NS[a]	DNA adducts	–	Peluso et al. 1998
Mouse (male germ cells)	98.7%	Dominant lethal mutation	–	EPA 1992j

[a]Test substance: glyphosate isopropylamine salt.

– = negative result; + = positive result; DNA = deoxyribonucleic acid; NS = not specified

1

Table 2-12. Genotoxicity of Glyphosate Formulations *In Vitro*

Test system	Glyphosate formulation	End point	Result: Activation: With	Result: Activation: Without	Reference
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Roundup (composition NS)	Gene mutation	–	–	Moriya et al. 1983
S. typhimurium TA98	Roundup (48% glyphosate isopropylamine salt)	Gene mutation	–	(+)[a]	Rank et al. 1993
S. typhimurium TA100	Roundup (48% glyphosate isopropylamine salt)	Gene mutation	(+)[b]	–	Rank et al. 1993
S. typhimurium TA98, TA100	Commercial formulation (NS)	Gene mutation	–	–	Wildeman and Nazar 1982
Escherichia coli WP2 *hcr*	Roundup (NS)	Gene mutation	–	–	Moriya et al. 1983
Bovine peripheral blood lymphocytes	Glyphosate (62% isopropylamine salt)	Chromosomal aberrations	NT	–	Holečková 2006
Bovine peripheral blood lymphocytes	Glyphosate (62% isopropylamine salt)	Chromosomal aberrations	NT	–	Šiviková and Dianovskỳ 2006
Human peripheral blood lymphocytes	Roundup (glyphosate isopropylamine salt; percentage NS)	Sister chromatid exchange	NT	(+)	Vigfusson and Vyse 1980

Table 2-12. Genotoxicity of Glyphosate Formulations *In Vitro*

Test system	Glyphosate formulation	End point	Result: Activation With	Result: Activation Without	Reference
Human peripheral blood lymphocytes	Roundup (30.4% glyphosate)	Sister chromatid exchange	NT	+	Bolognesi et al. 1997
Bovine peripheral blood lymphocytes	Glyphosate (62% isopropylamine salt)	Sister chromatid exchange	+	+	Šiviková and Dianovskỳ 2006
Human-derived buccal epithelial cells	Roundup (45% glyphosate acid)	Micronuclei	NT	+	Koller et al. 2012
Bovine peripheral blood lymphocytes	Glyphosate (62% isopropylamine salt)	Micronuclei	NT	(+)	Piešová 2004
Bovine peripheral blood lymphocytes	Glyphosate (62% isopropylamine salt)	Micronuclei	NT	(+)	Piešová 2005
Human GM38 cells	Glyphosate (NS)	DNA damage	NT	+	Monroy et al. 2005
Human HT1080 (fibrosarcoma) cells	Glyphosate (NS)	DNA damage	NT	+	Monroy et al. 2004, 2005
Human liver HepG2 cells	Grands Travaux (40% glyphosate)	DNA damage	NT	(+)	Gasnier et al. 2009
Chinese hamster ovary cells	Glyphosate (NS)	DNA damage	NT	+	Monroy et al. 2004
E. coli PQ37	Roundup (NS)	DNA damage	NT	+	Raipulis et al. 2009

[a]Weakly positive at 360 µg/plate in one test (4-fold increase in revertants/plate) but not in another test; cytotoxicity at concentrations ≥360 µg/plate.
[b]Weakly positive at 720 µg/plate (3.3-fold increase in revertants/plate); cytotoxicity at concentrations ≥360 µg/plate.

– = negative result; + = positive result; (+) = weakly positive result; NS = not specified; NT = not tested

1

Table 2-13. Genotoxicity of Glyphosate Formulations *In Vivo*

Species (test system)	Test substance (purity)	End point	Result	Reference
Drosophila (sex-linked recessive lethal mutation assay)	Roundup (glyphosate isopropylamine salt; purity NS)	Gene mutation	+	Kale et al. 1995
Drosophila (somatic mutation assay)	Roundup (NS)	Gene mutation	+	Ramos-Morales et al. 2008
Mouse (bone marrow)	Roundup (9.8% active ingredient)	Chromosomal aberrations	–	Dimitrov et al. 2006
Mouse (bone marrow)	Roundup (>41% glyphosate isopropylamine salt)	Chromosomal aberrations	+	Prasad et al. 2009
Mouse (bone marrow)	Roundup (48% glyphosate isopropylamine salt)	Micronuclei	–	Rank et al. 1993

Table 2-13. Genotoxicity of Glyphosate Formulations *In Vivo*

Species (test system)	Test substance (purity)	End point	Result	Reference
Mouse (bone marrow)	Roundup (30.4% glyphosate)	Micronuclei	+	Bolognesi et al. 1997
Mouse (bone marrow)	Roundup (9.8% glyphosate)	Micronuclei	–	Dimitrov et al. 2006
Mouse (bone marrow)	Roundup (>41% glyphosate isopropylamine salt)	Micronuclei	+	Prasad et al. 2009
Mouse (bone marrow)	Roundup (48% glyphosate isopropylammonium salt; 12% polyoxyethylene amine)	Micronuclei	–	Grisolia 2002
Mouse (bone marrow)	Roundup (NS)	Micronuclei	+	Rodrigues et al. 2011
Mouse (liver DNA)	Roundup (30.4% glyphosate)	DNA damage	+	Bolognesi et al. 1997
Mouse (kidney DNA)	Roundup (30.4% glyphosate)	DNA damage	+	Bolognesi et al. 1997
Mouse (liver DNA	Roundup (30.4% glyphosate)	Oxidative DNA damage	–	Bolognesi et al. 1997
Mouse (kidney DNA)	Roundup (30.4% glyphosate)	Oxidative DNA damage	+	Bolognesi et al. 1997
Mouse (liver, kidney DNA)	Roundup (30.4% glyphosate isopropylammonium salt)	DNA adducts	+	Peluso et al. 1998

+ = positive result; – = negative result; DNA = deoxyribonucleic acid; NS = not specified

Glyphosate Technical. Glyphosate did not induce gene mutations either with or without exogenous metabolic activation in numerous bacterial assays, or in assays using mammalian cells (EPA 1992i, Kubo et al. 2002; Li and Long 1988; NTP 1992). Lioi et al. (1998a, 1998b) reported concentration-related significant increases in chromosomal aberrations in human and bovine peripheral blood lymphocytes exposed to glyphosate, although concomitant decreases in mitotic index were indicative of some degree of cytotoxicity at least at the highest glyphosate concentrations. Mañas et al. (2009) found no evidence of glyphosate-induced chromosomal aberrations in human peripheral blood lymphocytes. Glyphosate was positive for induction of sister chromatid exchange in one assay using human peripheral blood lymphocytes (Bolognesi et al. 1997); weakly positive responses were obtained in other assays using human lymphocytes (Lioi et al. 1998a) and bovine lymphocytes (Lioi et al. 1998b). There was some evidence of cytotoxicity in the assays of Lioi et al. (1998a, 1998b). Glyphosate did not induce micronuclei in human peripheral blood lymphocytes exposed to glyphosate in the absence of exogenous

metabolic activation; an equivocal result was obtained in the presence of exogenous metabolic activation (Mladinic et al. 2009a, 2009b). The result was considered equivocal due to significant apoptosis at concentrations resulting in significantly increased micronuclei frequency. Koller et al. (2012) reported significantly increased frequency of micronuclei in an assay using human-derived buccal epithelial cells exposed to glyphosate. Roustan et al. (2014) reported significantly increased micronuclei frequency in Chinese hamster ovary K1 cells exposed to glyphosate without (but not with) exogenous metabolic activation. Negative results were obtained in an assay that evaluated the potential for glyphosate to induce unscheduled DNA synthesis in rat hepatocytes (Li and Long 1988). Mañas et al. (2009) and Lueken et al. (2004) reported positive results for DNA damage in glyphosate-exposed human peripheral blood lymphocytes. Exposure concentration-related significantly increased frequency of DNA damage was observed in another assay of glyphosate-exposed human peripheral blood lymphocytes, although significant apoptosis observed at all concentrations resulting in increased DNA damage (Mladinic et al. 2009a). Alvarez-Moya et al. (2014) reported DNA damage in human fibroblast CM5757 cells exposed to glyphosate technical.

The genotoxicity of glyphosate technical has been evaluated in a number of *in vivo* tests. Glyphosate did not induce chromosomal aberrations in bone marrow cells from rats administered glyphosate via intraperitoneal injection at 1,000 mg/kg (Li and Long 1988). Glyphosate did not increase the frequency of micronuclei in bone marrow cells from B6C3F1 mice administered glyphosate in the diet for 13 weeks at concentrations resulting in estimated doses as high as 10,780–11,977 mg/kg/day (NTP 1992) or other mice administered glyphosate (as isopropylammonium salt) via two intraperitoneal injections 24 hours apart (Rank et al. 1993). Kier and Kirkland (2013) summarized results from 10 industry studies that evaluated frequency of micronuclei in bone marrow cells from mice or rats administered glyphosate orally or via intraperitoneal injection; results were consistently negative for glyphosate-induced micronuclei, although an inconclusive result was determined for one study. However, other investigators reported positive results for micronuclei induction in bone marrow cells from mice administered glyphosate via intraperitoneal injection by single 300 mg/kg dose (Bolognesi et al. 1997) or two 200 mg/kg doses 24 hours apart (Mañas et al. 2009). Bolognesi et al. (1997) reported significantly increased frequency of DNA damage (single strand breaks) in liver and kidney and significantly increased frequency of oxidative DNA damage in liver (but not kidney) from mice administered glyphosate via single intraperitoneal injection at 300 mg/kg. Peluso et al. (1998) found no evidence of the formation of DNA adducts in liver or kidney from mice following intraperitoneal injection of glyphosate (as isopropylammonium salt) at up to 270 mg/kg.

Glyphosate Formulations. Glyphosate formulations (active ingredient ranging from approximately 30 to 62% of the formulation) were not mutagenic to bacterial test systems in available published studies (Moriya et al. 1983; Wildeman and Nazar 1982), numerous unpublished industry studies summarized by Kier and Kirkland (2013), or several other studies summarized by Williams et al. (2000). Weakly positive results were obtained for *Salmonella typhimurium* strain TA98 in the absence (but not presence) of exogenous metabolic activation and strain TA100 in the presence (but not absence) of exogenous metabolic activation (Rank et al. 1993); however, the positive responses were observed at concentrations exhibiting cytotoxicity and in only one of two tests in strain TA98. A Roundup formulation (described as 62% glyphosate isopropylamine salt) did not induce chromosomal aberrations in bovine peripheral blood lymphocytes in two assays that employed 24-hour exposures (Holečková 2006; Šiviková and Dianovský 2006); however, a significant increase in sister chromatid exchange was noted both with and without exogenous metabolic activation (Šiviková and Dianovský 2006). A slight, (statistically significant) 1.1–1.3-fold increase in frequency of sister chromatid exchange was observed in human peripheral blood lymphocytes exposed to a Roundup formulation that included an unspecified proportion of glyphosate as the isopropylamine salt (Vigfusson and Vyse 1980). Bolognesi et al. (1997) reported significantly increased sister chromatid exchange (1.3–1.5-fold greater than that of controls) in human peripheral blood lymphocytes exposed to a Roundup formulation (30.4% glyphosate; other components not specified) for 72 hours at concentrations of 0.1 and 0.33 mg/mL. The magnitude of this effect was comparable to that obtained using analytical-grade glyphosate at 10 times the concentration of the Roundup formulation, indicating that other substances in the Roundup formulation may have been at least partly responsible for the effect. In two assays, Roundup formulation (62% glyphosate isopropylamine salt) induced micronuclei in cultured bovine peripheral blood lymphocytes at noncytotoxic concentrations (Piešová 2004, 2005). Koller et al. (2012) reported significantly increased numbers of micronuclei in human-derived buccal epithelial cells exposed to a Roundup formulation (45% glyphosate acid) for 20 minutes, including concentrations that were noncytotoxic; this effect was more pronounced than that resulting from similar treatment using analytical grade glyphosate. A weakly positive result for DNA damage was reported for human liver HepG2 cells exposed to a Roundup formulation that contained 40% glyphosate (Gasnier et al. 2009). Exposure to non-specified concentrations of glyphosate resulted in treatment-related DNA damage in *Escherichia coli* PQ37 cells (Raipulis et al. 2009), human GM38 cells (Monroy et al. 2005), human HT1080 (fibrosarcoma) cells (Monroy et al. 2004, 2005), and Chinese hamster ovary cells (Monroy et al. 2004).

Several studies were designed to evaluate the genotoxicity of selected glyphosate formulations *in vivo*. Roundup of unspecified composition induced mutations in *Drosophila* in a sex-linked recessive lethal

mutation assay (Kale et al. 1995) and a somatic mutation assay (Ramos-Morales et al. 2008). The potential for selected Roundup formulations to induce chromosomal aberrations and/or micronuclei in bone marrow cells has been assessed in several studies in which test chemical was administered to mice via intraperitoneal injection. Roundup (9.8% active ingredient) did not induce chromosomal aberrations or micronuclei in mice administered the test chemical at one-half the LD_{50} (1,080 mg/kg) (Dimitrov et al. 2006). Although administration of a Roundup formulation (>41% glyphosate isopropylamine salt) at 25 and 50 mg/kg resulted in significantly increased frequencies of chromosomal aberrations and micronuclei, both doses appeared to be cytotoxic, as indicated by time- and dose-related significant decreases in mitotic indices (Prasad et al. 2009). Rodrigues et al. (2011) reported significantly increased micronucleus frequency at doses of 0.754 and 1.28 mg/kg for a Roundup formulation presumed to have contained 48% glyphosate as active ingredient; the response was as pronounced as that of a positive control substance (250 mg cyclophosphamide/kg). A Roundup formulation containing 30.4% glyphosate isopropylammonium salt induced micronuclei in bone marrow from mice administered the chemical via intraperitoneal injection at 300 mg/kg (expressed as glyphosate) (Bolognesi et al. 1997). Negative results were reported in two other studies that evaluated micronuclei induction in bone marrow cells from mice treated by intraperitoneal injection of Roundup formulations containing 48% glyphosate isopropylamine salt (Grisolia 2002; Rank et al. 1993). In the study of Grisolia (2002), polyoxyethylene amine surfactant accounted for 12% of the formulation. A Roundup formulation containing 30.4% glyphosate isopropylammonium salt induced single-strand breaks in DNA from liver and kidney of mice administered the chemical via intraperitoneal injection at 300 mg/kg (expressed as glyphosate) and oxidative DNA damage in kidney (but not liver) cells (Bolognesi et al. 1997). Peluso et al. (1998) reported the formation of DNA adducts in liver and kidney from mice following intraperitoneal injection of a Roundup formulation (30.4% glyphosate isopropylammonium salt) at doses in the range of 122–182 mg active ingredient/kg. The DNA adduct formation was considered likely related to other components of the Roundup formulation because DNA adduct formation was not observed in mice similarly treated with analytical-grade glyphosate at 270 mg/kg.

Exposure to glyphosate-containing products and evidence of genetic damage was reported in limited human studies. At 2 weeks to 2 months following aerial applications of glyphosate formulations in a region of northern Ecuador, DNA damage (strand breaks) was reported in blood samples collected from 24 area residents (Paz-y-Miño et al. 2007). Evaluation of 92 individuals from 10 communities near the northern Ecuador border at 2 years following the last aerial applications of glyphosate-containing herbicides revealed no evidence of exposure-related chromosomal damage (Paz-y-Miño et al. 2011). Bolognesi et al. (2009) reported increases in micronuclei in peripheral blood lymphocytes from nearby

residents following aerial spraying of glyphosate-based formulation with adjuvant to coca and poppy crops, or without adjuvant on sugar-cane plantations.

Additional unpublished genotoxicity assays were submitted to EPA and/or the European Commission (EC) during re-registration of products containing glyphosate. Most agencies, organizations, and/or expert panels have reviewed available genotoxicity data and concluded that the data do not support a genotoxicity role for glyphosate, at least at concentrations relevant to human exposure (e.g., APVMA 2017; Brusick et al. 2016; EPA 2016a; Kier and Kirkland 2013; NZ EPA 2016; FAO and WHO 2016). However, IARC (2015, 2016) concluded that there is strong evidence for the genotoxicity of glyphosate.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Toxicokinetic data for glyphosate are summarized below.

- Glyphosate is readily absorbed from the gastrointestinal tract; very little glyphosate is absorbed through the skin; it is assumed that glyphosate is readily absorbed from the respiratory tract.
- Absorbed glyphosate is readily distributed via the blood, but does not accumulate in any particular organ or tissue.
- Glyphosate does not undergo significant metabolism in mammals; <1% is metabolized to AMPA.
- Approximately two-thirds of an oral dose of glyphosate is excreted in the feces as unabsorbed parent compound. Most absorbed glyphosate is rapidly excreted in the urine as parent compound.

3.1.1 Absorption

3.1.1.1 Inhalation Exposure

Limited information is available regarding the toxicokinetics of inhaled glyphosate. Observations of increased urinary glyphosate levels among 48 farmer-applicators following application of Roundup is evidence that inhaled glyphosate can be absorbed (Acquavella et al. 2004). However, dermal absorption was likely involved in some cases because mean urinary glyphosate was higher among those farmers (14/48) who did not use rubber gloves. Detectable levels of urinary glyphosate were also measured in children of the farmers who were present during mixing, loading, or application of the herbicide; exposures among the children may have involved inhalation and/or dermal routes. No information was located regarding the toxicokinetics of inhaled glyphosate in among laboratory animals.

3.1.1.2 Oral Exposure

Information regarding the toxicokinetics of ingested glyphosate in humans is limited. The detection of glyphosate in serum and/or urine samples from individuals who had intentionally or unintentionally ingested glyphosate-containing products is confirmation of absorption from the gastrointestinal tract (e.g., Hiraiwa et al. 1990; Hori et al. 2003; Sribanditmongikol et al. 2012; Zouaoui et al. 2013). Numerous reports of systemic effects following intentional or unintentional ingestion of glyphosate-containing products serve as additional evidence that ingested glyphosate is absorbed (e.g., Chang and

Chang 2009; Chen et al. 2009; Hsiao et al. 2008; Kim et al. 2014; Lee et al. 2000; Menkes et al. 1991; Moon and Chun 2010; Roberts et al. 2010; Sato et al. 2011; Sawada et al. 1988; Sørenson and Gregersen 1999; Stella and Ryan 2004; Talbot et al. 1991; Tominack et al. 1991).

Several groups of investigators have evaluated the absorption of glyphosate following oral exposure of laboratory animals, particularly rats. In one study (NTP 1992), male F344/N rats were administered a single gavage dose of ^{14}C-glyphosate (purity 99%) in distilled water at 5.6 or 56 mg/kg. Other rats were administered a single dose of glyphosate at 5.6 mg/kg via intravenous injection, intraperitoneal injection, or oral (gavage) to compare 24-hour urinary and fecal elimination by these administration routes. Results from comparative studies of oral, intravenous, and intraperitoneal administration of glyphosate indicated that urinary radioactivity represented the amount of glyphosate absorbed and fecal radioactivity represented the amount of unabsorbed glyphosate following oral exposure. Although quantitative data were not included in the study report, the study authors estimated that 30% of the 5.6 mg/kg dose of ^{14}C-glyphosate was absorbed and that a relatively higher percentage of the 56 mg/kg dose was absorbed. In another study, male Sprague-Dawley rats were single gavage dose of ^{12}C- and ^{14}C-glyphosate at 10 mg/kg (Brewster et al. 1991). Based on urinary radioactivity, it was estimated that 35–40% of the oral dose had been absorbed from the gastrointestinal tract. Anadón et al. (2009) reported an absorption half-life of 2.29 hours following administration of an oral dose of 400 mg glyphosate/kg to rats; an estimated peak plasma glyphosate of 4.62 µg/mL was reached at 5.16 hours postdosing. Results from a number of unpublished industry studies cited in EPA (1993), IPCS (1994), and/or Williams et al. (2000), but not publicly available, demonstrate that single or repeated oral dosing of glyphosate to rats at doses in the range of 10–1,000 mg/kg/day result in urinary excretion of 14–36% of the administered dose during up to 7 days of posttreatment, which presumably represents the proportion of absorbed glyphosate.

3.1.1.3 Dermal Exposure

In vitro studies using human skin samples indicate that dermal penetration of glyphosate is very low. Wester et al. (1996) applied 300 µL of a 1% aqueous dilution of analytical-grade ^{14}C-labeled glyphosate to human cadaver skin (0.8 cm^2 of available skin area). The study authors reported a permeability constant of 4.59x10^{-4} cm/hour, with a lag time of 10.48 hours, which resulted in a calculated flux of 4.12 µg glyphosate/hour. Wester et al. (1991) used a ^{14}C-labeled Roundup formulation (1.1 mg glyphosate/mL) to evaluate dermal absorption of glyphosate through human skin (*in vitro*) and abdominal skin of Rhesus monkeys (*in vivo*). Undiluted application to human skin samples at doses ranging from 15.4 to 154 µg/cm^2 resulted in 0–0.4% dermal absorption over 8 hours postapplication; dermal absorption

of glyphosate from aqueous dilutions of test substance (1:20 or 1:32 test substance:water, v/v) during 16 hours postapplication was ≤2.2%. Twelve-hour *in vivo* application of the test substance diluted 1:29 with water at concentrations of 25 or 270 μg/cm^2 resulted in 7-day recovery of 2.2 and 0.8 % of the applied dose, respectively, in the urine and 3.6 and 0.7%, respectively, in the feces. These results indicate that approximately 3–4% of the applied dose had been absorbed.

3.1.2 Distribution

3.1.2.1 Inhalation Exposure

No human or animal data were located regarding distribution of glyphosate following absorption via the inhalation exposure route.

3.1.2.2 Oral Exposure

No human data were located regarding distribution of glyphosate following absorption via the oral exposure route.

In male F344/N rats administered single gavage dose of ^{14}C-glyphosate (purity 99%) in distilled water at 5.6 or 56 mg/kg, peak blood radioactivity occurred at 1 and 2 hours postdosing, respectively, mean peak blood concentration was 30-fold higher in the high-dose group (NTP 1992). Among rats gavaged at 5.6 mg radiolabeled glyphosate/kg and evaluated for tissue distribution, total tissue radioactivity amounted to approximately 12, 11.7, 5.5, 0.9, and 0.1% of the administered dose at 3, 6, 12, 24, and 96 hours postdosing, respectively. The highest radioactivity level was found in the small intestine, reaching a peak level of approximately 10% of the administered dose at 6 hours postdosing; radioactivity in the large intestine peaked at approximately 1.2% at 3 hours postdosing. Liver, kidney, skin, and blood each accounted for <1% of the administered dose at each time point. By 24 hours postdosing, <1% of the administered dose remained in all tissues combined. Brewster et al. (1991) administered ^{12}C- and ^{14}C-glyphosate by single gavage dose at 10 mg/kg to male Sprague-Dawley rats and found approximately 34% of the administered dose in the small intestine (not associated with intestinal content) at 2 hours postdosing, decreasing to 0.05% of the administered dose by 96 hours postdosing. Radioactivity levels in most other tissues (blood, colon, kidney, liver, stomach, abdominal fat, testicular fat) peaked at 2–6 hours postdosing; each of these tissues accounted for ≤1.3% of the administered dose at peak and ≤0.06% by 96 hours postdosing. Radioactivity in bone peaked at 6 hours postdosing (4.7% of the administered dose) and remained at 1.7% at 96 hours postdosing. The tissue to blood ratio for bone increased with time

suggesting a slower elimination from bone compared to blood. Anadón et al. (2009) reported an absorption half-life of 2.29 hours following administration of an oral dose of 400 mg glyphosate/kg to rats; an estimated peak plasma glyphosate of 4.62 μg/mL was reached at 5.16 hours postdosing.

3.1.2.3 Dermal Exposure

No human data were located regarding distribution following dermal exposure to glyphosate.

Limited animal data are available. The observation of radioactivity in urine and feces collected from rhesus monkeys following dermal application of a ^{14}C-labeled Roundup formulation (1.1 mg glyphosate/mL; diluted 1:29 with water) is demonstration of systemic distribution following dermal absorption (Wester et al. 1991). However, at sacrifice 7 days posttreatment, no radioactivity was detected in spleen, ovaries, kidney, brain, abdominal fat, bone marrow, upper spinal column, or central nervous fluid.

3.1.2.4 Other Routes of Exposure

Male and female Sprague-Dawley rats were administered ^{14}C-glyphosate via intraperitoneal injection at 1,150 mg/kg (EPA 1992h). Radioactivity measured in bone marrow samples taken 30 minutes postinjection amounted to approximately 0.0044 and 0.0075% of the administered activity for the males and females, respectively. Anadón et al. (2009) administered glyphosate (95% purity) to male Wistar rats via intravenous injection at 100 mg/kg. Plasma levels of glyphosate and its metabolite, AMPA, were measured using high-performance liquid chromatography (HPLC). Reported fast plasma distribution (half-life of 0.345 hours) and high volume of distribution at steady state (2.99 L/kg) were interpreted to indicate that glyphosate was extensively distributed to extravascular tissues.

3.1.3 Metabolism

Glyphosate does not undergo significant metabolism in mammals. Available data are limited to the oral exposure route and indicate that ingested glyphosate is eliminated mostly as parent compound; only a small amount may be metabolized to AMPA. Figure 3-1 depicts the chemical structures of glyphosate and AMPA. In one human case of intentional ingestion of an herbicide in a suicide attempt, glyphosate and its metabolite, AMPA, were detected in serum and urine (Hori et al. 2003). At 16 hours postingestion, serum levels of glyphosate and AMPA were 4.4 and 0.03 μg/mL, respectively (147:1,

glyphosate:AMPA). Total urinary excretion of glyphosate and its metabolite during 4 days postingestion was 3.7 g and 25 mg, respectively (148:1, glyphosate:AMPA).

Figure 3-1. Chemical Structures of Glyphosate and Aminomethylphosphonic Acid (AMPA)

Glyphosate Aminomethylphosphonic acid (AMPA)

Results from available animal studies also indicate that very little ingested glyphosate is metabolized. Anadón et al. (2009) administered glyphosate (95% purity) to male Wistar rats by gavage at 400 mg glyphosate/kg. Plasma glyphosate peaked at 5.16 hours postdosing and measured 4.62 µg/mL; plasma AMPA peaked at 2.42 hours postdosing and measured 0.416 µg/mL. Based on the ratios between the area under the curve (AUC) for AMPA and the AUC for glyphosate, it was estimated that the metabolite represented 6.49% of the parent compound plasma concentration. In an unpublished study summarized by EPA (1993) and Williams et al. (2000), following oral administration of radiolabeled glyphosate (>99% purity) to Sprague-Dawley rats at 10 mg/kg, the glyphosate metabolite (AMPA) was detected in the urine (0.2–0.3% of the administered dose) and feces (0.2–0.4% of the administered dose). The formation of AMPA was thought to have occurred in the gastrointestinal tract (possibly by microflora) because AMPA was not detected in other rats administered glyphosate via intravenous injection. Following a single gavage dose of administered radiolabeled glyphosate (>99% purity) to Sprague-Dawley rats, expired air accounted for <0.27% of the administered radioactivity at 24 hours postdosing, indicating that glyphosate metabolism had occurred to a slight extent (EPA 1993).

3.1.4 Excretion

3.1.4.1 Inhalation Exposure

Limited information is available regarding elimination and excretion of glyphosate following inhalation exposure. In one study, urinary glyphosate levels were evaluated in 48 farmer-applicators prior to application of Roundup, immediately following application, and for 3 days thereafter. Urinary glyphosate was detectable in 15% (7/47) of the farmers prior to Roundup application, in 60% (29/48) of the farmers

immediately following application, and in only 27% (13/48) of the farmers on postapplication day 3. No information was located regarding elimination or excretion following inhalation exposure of laboratory animals to glyphosate.

3.1.4.2 Oral Exposure

Glyphosate has been detected in feces and urine of individuals who intentionally or accidentally ingested relatively large amounts of glyphosate. However, no quantitative data were located regarding elimination and excretion in humans following oral exposure to glyphosate.

Results from animal studies identify the feces and urine as major routes of elimination following oral exposure to glyphosate. For example, among male and female Sprague-Dawley rats administered ^{14}C-glyphosate (99% purity) via single gavage dose at 10 mg/kg, during 7 days posttreatment, radioactivity recovered in the feces averaged 62.4 and 69.4% of the administered dose (males and females, respectively); another 28.6 and 22.5% of the administered dose (males and females, respectively) was recovered in the urine (IPCS 1994). Thus, feces and urine accounted for approximately 88–91% of the administered dose. HPLC analysis revealed that parent compound accounted for 98.5–99.3% of the radioactivity in feces and urine. There were no significant differences in fecal and urinary excretion among rats dosed with unlabeled glyphosate for 14 days followed by a single oral dose of radiolabeled glyphosate. Following single gavage dosing of ^{14}C-glyphosate (>96% purity) to male and female Sprague-Dawley rats at 30 mg/kg, the feces accounted for 57–59% of the administered radioactivity and the urine accounted for 27–29% during the first 36 hours posttreatment; indicating that fecal and urinary excretion occur relatively rapidly following oral exposure to glyphosate (IPCS 1994). In male F344/N rats administered single gavage dose of ^{14}C-glyphosate (purity 99%) in distilled water at 5.6 or 56 mg/kg, 72-hour collection of feces and urine resulted in the recovery of 91–92% of the administered radioactivity; 74 and 19%, respectively, at the low dose and 58 and 34%, respectively, at the high dose (NTP 1992). Very little ingested glyphosate is eliminated via routes other than feces and urine. Among Sprague-Dawley rats administered radiolabeled glyphosate (>99% purity) by single gavage dose, <0.27% of the administered radioactivity was recovered in expired air at 24 hours postdosing (EPA 1993).

3.1.4.3 Dermal Exposure

No information was located regarding elimination or excretion following known dermal exposure to glyphosate in humans. However, in a study that evaluated urinary glyphosate levels in 48 farmer-applicators involved in application of Roundup, mean urinary glyphosate was higher among those farmers

(14/48) who did not use rubber gloves, indicating that some glyphosate had been absorbed through the skin (Acquavella et al. 2004). Limited information is available for laboratory animals. Wester et al. (1991) applied a ^{14}C-labeled Roundup formulation (1.1 mg glyphosate/mL; diluted 1:29 with water) to evaluate dermal absorption of glyphosate through abdominal skin of Rhesus monkeys (*in vivo*). Twelve-hour application of the test substance at concentrations of 25 or 270 μg/cm^2 resulted in 7-day recovery of 2.2 and 0.8% of the applied dose, respectively, in the urine and 3.6 and 0.7%, respectively, in the feces.

3.1.4.4 Other Routes of Exposure

Male and female Sprague-Dawley rats were administered ^{14}C-glyphosate via intraperitoneal injection at 1,150 mg/kg (EPA 1993). Assuming first-order kinetics, the half-life of elimination from the bone marrow was estimated at 7.6 and 4.2 hours for the males and females, respectively. A half-life for elimination of radioactivity from plasma was approximately 1 hour for both sexes. These results indicate that glyphosate reaching the blood was rapidly eliminated and that the small fraction reaching bone marrow was rapidly eliminated. Anadón et al. (2009) reported a half-time of 9.99 hours for elimination of glyphosate from the blood of male Wistar rats administered glyphosate (95% purity) via intravenous injection at 100 mg/kg.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

PBPK models for glyphosate were not located.

3.1.6 Animal-to-Human Extrapolations

No information was located to suggest significant differences between animals and humans regarding glyphosate toxicity.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to glyphosate are discussed in Section 5.7, Populations with Potentially High Exposures.

No information was located to indicate significant age- or gender-related differences in susceptibility to glyphosate toxicity.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to glyphosate are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure

of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for glyphosate from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by glyphosate are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

The presence of glyphosate in blood or urine is a reliable biomarker of exposure to glyphosate-containing substances. Very small amounts of the glyphosate metabolite (AMPA) might be detected in blood or urine; however, most absorbed glyphosate is excreted unchanged.

3.3.2 Biomarkers of Effect

No information was located regarding biomarkers of effect specific to glyphosate toxicity.

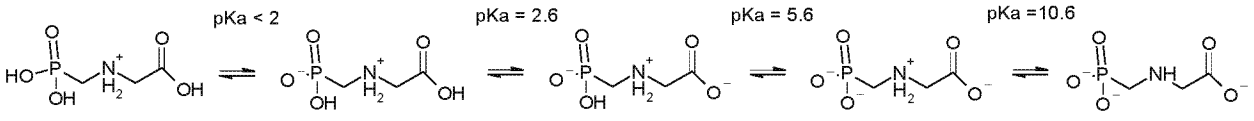
3.4 INTERACTIONS WITH OTHER CHEMICALS

Surfactants such as POEA in glyphosate-containing products might enhance the toxicity of glyphosate; results from one study indicate that the surfactant may be more acutely toxic than glyphosate or the combination of glyphosate and POEA (Adam et al. 1997).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Glyphosate is an organic acid composed of a phosphonomethyl and glycine component. The chemical name for glyphosate is *N*-(phosphonomethyl) glycine. Glyphosate is a zwitterion with four distinct dissociation constants (pKa values are depicted below) and exists as different ionic species depending on the pH of its surroundings. Glyphosate is an amphoteric chemical and may react as an acid or a base under certain conditions.



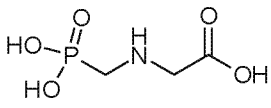
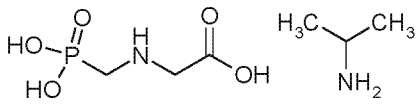
Glyphosate isopropylamine (Chemical Abstracts Registry Number [CASRN] 38641-94-0) is one of the salt forms of glyphosate used in commercial herbicides employing glyphosate as an active ingredient. This substance is registered as a pesticide by the EPA (1993) and is used to control broadleaf weeds and grasses; in food and nonfood settings, flower gardens, lawns, turf, residential areas, and forests; and along roadsides.

Detailed information on the chemical identity of glyphosate and glyphosate isopropylamine is provided in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Detailed information on the physical and chemical properties of glyphosate and glyphosate isopropylammonium is provided in Table 4-2.

Table 4-1. Chemical Identity of Glyphosate and Glyphosate Isopropylamine[a]

Characteristic	Information	
Chemical name	Glyphosate	Glyphosate isopropylamine
Synonym(s)	Glyphosphate; N-(phosphonomethyl) glycine; phosphonomethyliminoacetic acid; glyphosate acid	Glycine, N-(phosphonomethyl)-, compound with 2-propanamine (1:1); glyphosate-isopropylammonium; glyphosate mono(isopropylamine) salt; glyphosate-mono(isopropylammonium); N-(phosphonomethyl)glycine, isopropylamine salt
Registered trade name(s)	Pondmaster; Roundup Max; Glifoglex; Glycel; Muster; Rondo; Sonic; Spasor; Sting; Tumbleweed; MON-0573; CP 67573	Roundup; Rondo; Rodeo; Glifonox; Glycel; MON-0139; CP 70139; Shackle[b]
Chemical formula	$C_3H_8NO_5P$	$C_3H_8NO_5P.C_3H_9N$
Chemical structure		
CAS Registry Number	1071-83-6	38641-94-0

[a]All information obtained from McBean (2011); O'Neil et al. (2013), and/or ChemIDplus (2017) unless noted otherwise.
[b]EPA 1993.

CAS = Chemical Abstracts Service

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Table 4-2. Physical and Chemical Properties of Glyphosate and Selected Salts[a]

Property	Glyphosate	Glyphosate isopropylamine salt
Molecular weight	169.1	228.2
Color	White	White
Physical state	Solid; crystals	Powder
Melting point	230°C (decomposes)	Two stages: 143–164 and189–223°C
Boiling point	No data	Decomposes without boiling
Density at 20°C	1.705	1.482
Odor	Odorless	Odorless
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water at 25°C	12,000 mg/L 10,500 mg/L (pH 1.9, 20°C)	1,050,000 mg/L (pH 4.3, 25°C)
Organic solvent(s)	Insoluble in most organic solvents: acetone, ethanol, and xylene	Dichloromethane 184 mg/L at 20°C; methanol 15,880 mg/L at 20°C
Dissociation constants:	pKa_1 0.8; pKa_2 3; pKa_3 6; pKa_4 11; pKa_1[b] <2; pKa_2[b] 2.6; pKa_3[b] 5.6; pKa_4[b] 10.6	pKa_1 2.18 at 20°C (monophosphate); pKa_2 5.77 at 20°C (carboxylic acid)
Partition coefficients:		
Log K_{ow}	<-3.4	-5.4
Log K_{oc}	3.4–3.7 (K_{oc}=2,600–4,900)[c]	No data
Vapor pressure at 25°C	$9.8x10^{-8}$	$1.58x10^{-8}$
Henry's law constant	$2.1x10^{-12}$ atm-m^3/mol at 25°C[d]	$3.3x10^{-15}$ atm-m^3/mol at 25°C[d]
Autoignition temperature	No data	No data
Flashpoint	Not flammable	No data
Flammability limits	No data	No data
Explosive limits	No data	No data

[a]All information obtained from either McBean (2011) or O'Neil et al. (2013).
[c]Glass 1987.
[b]Sprankle et al. 1975.
[d]EPI Suite 2012.

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CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Glyphosate has not been identified in any of the 1,832 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2015). However, the number of sites evaluated for glyphosate is not known.

- Occupational and residential exposure is a result of glyphosate's use in agricultural, non-agricultural, industrial, and residential settings. The highest potential for dermal, inhalation, and ocular exposure is expected for pesticide applicators, farm workers, and home gardeners who use herbicides containing glyphosate.

- The general population may be exposed to glyphosate via ingestion of crops, plants, and foods with residues of this chemical. Residential exposure may occur via dermal contact or inhalation through application of consumer products containing glyphosate or by coming into contact with crops or soils on which glyphosate-containing products have been applied.

- Occupational exposure of glyphosate may occur via dermal contact or inhalation during manufacture, transport, application, and disposal processes. Occupational exposure may occur via dermal and ocular routes from accidental splashes during mixing, loading, and application of herbicides containing glyphosate. Accidental oral exposure may occur via unintentional ingestion; however, oral exposure is expected to be minimal. Dermal contact appears to be the major route of exposure to glyphosate for individuals involved in its application.

- Glyphosate mainly enters the environment as a direct result of its herbicidal use. Fate of this chemical in the environment includes degradation, transport, and partitioning processes, which are governed by its physicochemical properties and by abiotic or biotic degradation under certain environmental conditions. Glyphosate is a nonvolatile, highly polar, non-residual herbicide that has low potential for environmental persistence and is unlikely to bioaccumulate.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 PRODUCTION

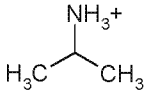
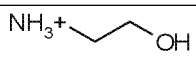
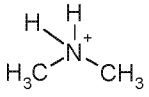
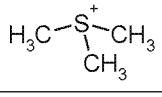
No information is available in the TRI database on facilities that manufacture or process glyphosate because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

Production of glyphosate is achieved through heating phosphorous acid and *a*-amino acetic acid followed by the addition of formaldehyde (Muller and Applebyki 2010). Glyphosate may also be produced by heating glycine and chloromethylphosphonic acid in aqueous sodium hydroxide (IPCS 1994).

Glyphosate is produced commercially in the United States as a technical-grade substance with a purity ≥95% (McBean 2011).

Glyphosate is typically manufactured for commercial use as a salt available in soluble liquid and soluble granule formulations. Salt forms of glyphosate include the isopropylamine salt, sodium salt, and monoammonium salt. Table 5-1 summarizes some of the common glyphosate salts that may be used as active ingredients in herbicides. Due to the various salt forms, the active ingredient listed on products is sometimes expressed in terms of acid equivalent.

Table 5-1. Glyphosate Salts

Name	CAS Registry Number	EPA PC Code	Cation	U.S. registration[a]
Glyphosate isopropylamine salt	38641-94-0	103601		Yes
Glyphosate mono ammonium	40465-66-5	103604	NH_4^+	Yes
Glyphosate ethanolamine salt	40465-76-7	103605		Yes
Glyphosate triammonium salt	114370-14-8	103607	NH_4^+	Yes
Glyphosate diammonium salt	69254-40-6	103607	NH_4^+	Yes
Glyphosate dimethylammonium salt	34494-04-7	103608		Yes
Glyphosate potassium salts	70901-12-1; 70901-20-1; 39600-42-5	103613	K^+	Yes
Glyphosate monosodium salt	34494-03-6	103603	Na^+	No
Glyphosate sesquisodium salt	70393-85-0	103603	Na^+	No
Glyphosate trimesium	81591-81-3	128501		No

[a]Pan 2014

CAS = Chemical Abstracts Service; EPA = U.S. Environmental Protection Agency; PC = pesticide chemical

Herbicide formulations employing glyphosate salts are commonly produced in combination with additives, inert ingredients, and surfactants. The salt derivatives enhance absorption of glyphosate from the surface of the plant or leaf structure, but are not the herbicidally active portion of the compound. Specific formulations vary in composition and are marketed under numerous trade names (PAN 2009). Polyoxyethylene amine (POEA) (CASRN 24911-53-5) is a surfactant used in the commercial product

Roundup (PAN 2009). Surfactants are used in herbicide formulations to increase penetration of glyphosate into plants. Sulfuric acid (CASRN 7664-93-9), phosphoric acid (CASRN 7664-38-2), propylene glycol (CASRN 57-55-6), and sodium benzoate (CASRN 532-32-1) are examples of additives used in some formulations (IPCS 1994; PAN 2009). Products may contain ingredients such as simazine (CASRN 122-34-9) and 2-methyl-4-chlorophenoxyacetic acid (CASRN 94-74-6). The ingredient 2,4-dichlorophenoxyacetic acid (CAS 94-75-7) may be present at concentrations ranging from 11.1 to 20.6% (IPCS 1994). Commercial products containing glyphosate may have concentrations ranging from 0.96 to 94 w/w%. The common herbicide, Roundup, has product formulations containing glyphosate concentrations ranging from 0.96 to 62.0 w/w% (IPCS 1994).

The introduction of glyphosate-resistant crops such as soy beans in 1996, canola and cotton in 1997, and maize in 1998, along with the distribution of their genetically engineered seeds, had major impacts on the production and demand for glyphosate.

According to the National Pesticide Information Retrieval System (NPIRS), as of May 2017, there were 43 companies manufacturing EPA federally registered products under the active pesticide code 417300 (glyphosate), which are available for use in the United States; see Table 5-2 (NPIRS 2017). In addition, there were 72 companies in the United States that were manufacturing chemicals under the active pesticide code 103601 (glyphosate isopropylamine salt) (NPIRS 2017).

Table 5-2. Companies Manufacturing Products Under Pesticide Code 417300

Company	Address	City, State, Zip Code
Syngenta Crop Protection, LLC	410 Swing Road	Greensboro, North Carolina 27419
The Scotts Company	D/B/A The Ortho Group, 14111 Scottslawn Road	Marysville, Ohio 43041
FMC Corporation, Agricultural Products Group	1735 Market Street	Philadelphia, Pennsylvania 19103
Monsanto Company	Chesterfield Village Research Center, 700 Chesterfield Parkway North	Chesterfield, Missouri 63017
Winfield Solutions, LLC	P.O. Box 64589	St. Paul, Minnesota 55164
ABC Compounding Co., Inc.	P.O. Box 16247	Atlanta, Georgia 30321
Cheminova A/S	P.O. Box 9	DK-7620 Lemvig
Helena Chemical, Co.	225 Schilling Boulevard, Suite 300	Collierville, Tennessee 38017
Chemsico, A Division of United Industries Corporation	P.O. Box 142642	St. Louis, Missouri 63114
Adama Agan Ltd	P.O. Box 262	Ashdod

Table 5-2. Companies Manufacturing Products Under Pesticide Code 417300

Company	Address	City, State, Zip Code
Drexel Chemical Company	P.O. Box 13327	Memphis, Tennessee 38113
Loveland Products, Inc.	P.O. Box 1286	Greeley, Colorado 80632
Nufarm Limited	103–105 Pipe Road	Laverton North, Victoria 3026 Australia
Albaugh, LLC	P.O. Box 2127	Valdosta, Georgia 31604
Atanor S.A.	Foreign Trade Department, Albarellos 4914	B1605 AFR, Munro, Providence de Buenos Aires
BASF Sparks, LLC	P.O. Box 13528	Research Triangle Park, North Carolina 27709
Control Solutions, Inc.	5903 Genoa-Red Bluff Road	Pasadena, Texas 77507
Tenkoz, Inc.	1725 Windward Concourse	Alpharetta, Georgia 30005
Dow AgroSciences, LLC	9330 Zionsville Rd 308/2e	Indianapolis, Indiana 46268
Makhteshim Agan of North America, Inc.	d/b/a Adama, 3120 Highwoods Boulevard, Suite 100	Raleigh, North Carolina 27604
United Phosphorus, Inc.	630 Freedom Business Center, Suite 402	King of Prussia, Pennsylvania 19406
Monsanto Company	Lawn & Garden Products, 600 13th Street, NW, Suite 660	Washington, DC 20005
Helm Agro US, Inc.	401 E. Jackson Street, Suite 1400	Tampa, Florida 33602
Mey Corporation	121 South Estes Drive, Suite 101	Chapel Hill, North Carolina 27514
Sharda Cropchem, Limited	Domnic Holm, 29th Road	Bandra (West), Mumbai 400050
Rotam Agrochemical Company, Ltd.	26/F, E-Trade Plaza, 24 Lee Chung Street	Chai Wan
Sharda USA LLC	P.O. Box 640	Hockessin, Delaware 19707
Ragan and Massey, Inc.	101 Ponchatoula Parkway	Ponchatoula Louisiana 70454
Tide International, USA, Inc.	21 Hubble	Irvine, California 92618
Agsaver II, LLC	P.O. Box 111	McGehee, Arkansas 71654
Repar-Glypho, LLC	8070 Georgia Avenue, Suite 209	Silver Spring, Maryland 20910
Farmway, Inc.	P.O. Box 640	Hockessin, Delaware 19707
Consus Chemicals, LLC	22 Pine Tree Drive	Wayne, New Jersey 07470
Axss Technical Holdings, LLC	111 Martin Road	Fulton, Mississippi 38843
Cinmax International, LLC	3050 Suite 113	Bloomington, Minnesota 55425
Agromarketing Co., Inc.	133 Mavety Street	Toronto, Ontario, Canada M6P
Glysorttech, LLC	281 Hampshire Drive	Plansboro, New Jersey 08536
Liberty Crop Protection, LLC	4850 Hahns Peak Drive, Suite 200	Loveland, Colorado 80538
Gly-Peak, LLC	224 South Bell Avenue	Ames, Iowa 60010
Tundra Agroindustrial, Ltd.	P.O. Box 10	Lemars, Iowa 51031
Argustoli H.C., LLC	10191 Park Run Drive, Suite 110	Las Vegas, Nevada 89145

Table 5-2. Companies Manufacturing Products Under Pesticide Code 417300

Company	Address	City, State, Zip Code
Genmerica NA LLC	P.O. Box 1603	Cheyenne, Wyoming
Gruhn Mill Crop Solutions, LLC	701 Fifth Avenue, Suite 6100	Seattle, Washington 98104

Source: NPIRS 2017

5.2.2 IMPORT/EXPORT

No information was found concerning U.S. imports and exports of glyphosate.

5.2.3 USE

Glyphosate is a phosphonoglycine herbicide, first registered for use by the EPA in 1974. In June 1986, glyphosate was issued a Registration Standard (EPA 1986c) requiring additional data, which included phytotoxicity, environmental fate, toxicology, product chemistry, and residue chemistry studies; reregistration of single active ingredient formulations, plus one additional active ingredient formulation, were finalized in 1993 (EPA 1993). Glyphosate is registered for pre- and post-emergent applications on various fruit, vegetable, and field crops, and as of December 2009, glyphosate is in the process of reregistration under the EPA's review process; docket ID: EPA-HQ-OPP-2009-0361 (EPA 2009b). Additionally, new registration requests for use on certain fruits and vegetables are being reviewed under EPA docket ID: EPA-HQ-OPP-2012-0132 (EPA 2012d).

Glyphosate is used as a non-selective contact herbicide. Formulations are applied directly to food crops and non-food field crops, and in non-crop areas such as roadsides and aquatic areas. Glyphosate is used in agriculture, forestry, industrial, lawn and garden, and aquatic environments for weed control. Glyphosate is applied to control broad-leaved weeds and woody brush, as well as annual and perennial grasses in various fruit- or nut-bearing trees and in cereal crops, peas, beans, oilseed rape, and mustard fields (Muller and Applebyke 2010; Plimmer et al. 2004). The sodium salt (CASRN 34494-03-6) can be used as a plant growth regulator for peanuts and sugarcane (EPA 1993). The majority of glyphosate is used on soybeans fields, corn fields, and hay pastures. Glyphosate is a foliar-applied herbicide. Before the introduction of genetically modified glyphosate-resistant crops, application generally occurred before crops were planted (Duke and Powles 2008). After successful production and approval of glyphosate-resistant crops, such as soybean, cotton, maize, and canola, application generally occurs after planting and before harvest; the timing depends on the specific application (Duke and Powles 2008; Muller and

Applebyke 2010). Application techniques include aerial treatments, typically used for large-scale purposes, and wiping equipment or spraying equipment attached to vehicles, generally used for small-scale applications (FAO 1997; IPCS 1994).

According to data from the Pesticide Action Network (PAN) Pesticide Database, there are 102 products containing glyphosate (CASRN 1071-83-6) as the active ingredient, 94 of which have active registrations in the United States. There are 848 products containing glyphosate isopropylamine salt (CASRN 38641-94-0) as the active ingredient, of which 739 have active registrations in the United States (PAN 2016a, 2016b).

The introduction of glyphosate-resistant crops and the distribution of their seeds in the mid 1990s increased the use of herbicidal products containing this chemical. Increasing trends can be seen in estimated annual agricultural use data for the United States from the National Water-Quality Assessment (NAWQA) Program. Estimated yearly usage increased from approximately 20 to 60 million pounds from 1992 to 1998, from approximately 70 to 130 million pounds from 1999 to 2003, from approximately 140 to 250 million pounds from 2004 to 2011, and steady use of approximately 285–290 million pounds from 2012 through 2014 (USGS 2017). The EPA recently granted the registration of a new herbicide named Enlist Duo™ containing 2,4-D choline salt and glyphosate for use on genetically modified corn and soybean crops designed to be resistant to 2,4-D and glyphosate (EPA 2014).

5.2.4 DISPOSAL

Wastes resulting from products containing glyphosate should be disposed of at an approved waste disposal facility or in landfills approved for pesticide disposal. Disposal practices should be in accordance with federal, state, and local procedures. Non-refillable containers should never be reused. Empty containers should be rinsed thoroughly and offered for recycling, if available, or disposed of in accordance with container labels. Rinse-water can be emptied into formulation equipment and applied as residual pesticide in the appropriate manner. Do not contaminate fresh waters when disposing of equipment wash waters or container rinse waters. Containers that have not been completely rinsed may be considered hazardous and should be disposed of with regard to federal, state, and local regulations. Any unused product may be recycled by applying the product in an approved use setting or returning it to the manufacturer or supplier for safe disposal (Agrisolutions 2010; EPA 1993, 2011).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

The use of glyphosate as an herbicide for crops and non-crop applications is the major source of glyphosate that intentionally enters the environment. Some glyphosate may be released from the manufacture, transport, and disposal of glyphosate or glyphosate-containing products. The majority of herbicidal formulations with glyphosate are directly applied to crops and soils intended for protection. Depending on its application, glyphosate may enter aquatic environments through direct application or as a result of overspray in areas near aquatic environments. Aerial applications of glyphosate may result in unintended transport, depending on application technique and meteorological conditions, such as wind drift (EPA 1993; IPCS 1994; PAN 2009; Yates et al. 1978).

5.3.1 Air

There is no information on releases of glyphosate to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Glyphosate released to the air from aerial and ground equipment has the potential for downwind transport. Yates et al. (1978) assessed the loss due to drift after application. The lowest drift losses resulted when ground sprayers operating at low pressure were employed. The highest drift losses occurred when jet nozzles were employed during aerial application performed by helicopter.

The Air Quality System (AQS) database is EPA's repository of criteria air pollutants and hazardous air pollutants (HAPs), containing monitoring data from >2,600 monitoring sites across the United States. Glyphosate has not been included in the AQS ambient air monitoring data as of 2016 (EPA 2017b).

5.3.2 Water

There is no information on releases of glyphosate to water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Glyphosate may enter surface water systems either directly as a result of its aquatic use or indirectly due to overspray near surface water. Limited amounts may enter surface waters indirectly due to transport of residues adsorbed to soil particles in run-off events.

5.3.3 Soil

There is no information on releases of glyphosate to soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Glyphosate is released to soils by direct ground application and spraying applications. Between 1989 and 1991, approximately 13–20 million agricultural and non-agricultural acres were treated with 18.7 million pounds of glyphosate (EPA 1993).

In the United States in 2007, agricultural application of glyphosate was approximately 82,800 metric tons and non-agricultural application of glyphosate was 9,300 metric tons (Battaglin et al. 2014). In 2010, a reported 764,826 pounds (1,933 tons) of glyphosate, 7,098,860 pounds (3,550 tons) of glyphosate as the isopropylamine salt, and 736,192 pounds (368 tons) of glyphosate as the potassium salt were applied in agricultural areas of California (Cal EPA 2010). The PAN reports detailed pesticide use data for California. The use of glyphosate as an herbicide for treating crops and for commodity fumigation was approximately 3,000 pounds (1.36 tons) in 2012; 475 acres were treated across 24 regions in California. Tulare County accounted for the majority of the usage at 865 pounds (0.4 tons). Use of glyphosate isopropylamine salt was 4,960,420 pounds (2,250 tons) in 2012, with 2,367,310 acres treated across 49 regions in California and use of glyphosate potassium salt was 5,364,090 pounds (2,300 tons) in 2012, with 3,126,040 acres treated across 49 regions in California. Additional pesticide use information from California for the years 2000–2012 may be directly assessed from the PAN Pesticide Database website http://www.pesticideinfo.org/ (PAN 2016a).

A 2008 survey of pesticide application in Ontario, Canada, conducted by the Ministry of Agriculture, Food, and Rural Affairs reported that glyphosate use increased from 1,170,762 kg active ingredient in 2003 up to 2,062,648 kg active ingredient in 2008 (OMAFRA 2008). A total of 527,952 kg of glyphosate were used on field crops, 6,700 kg were used on fruit, 6,110 kg were used on vegetables, and 6,635 kg of glyphosate were used on nursery crops, sod, and ginseng; greenhouse crops were not included. Specific crop use in 2008 for the amount of the active ingredient glyphosate applied as an herbicide equaled 527,952 kg on field corn, 1,253,773 kg on soybeans, 11,087 kg on canola, 155,428 kg on wheat, 9,206 kg on oats, 6,588 kg on barley, 6,167 kg on mixed grains, 3,185 kg on rye, 18,054 kg on white beans, 18,661 kg on dry beans, 27,011 kg on hay, 2,717 kg on pasture, 1,386 kg on sugar beets, and 1,991 kg on other field crops (OMAFRA 2008).

A 2013/2014 survey of pesticide application in Ontario, Canada, conducted by the Ministry of Agriculture, Food, and Rural Affairs reported pesticide use for glyphosate (OMAFRA 2015). A total of 2,909,184 kg of glyphosate were used on all surveyed field crops in 2013/2014; 13,194 kg were used on fruit and 9,869 kg were used on vegetables. Specific crop use in 2013 for the amount of the active ingredient glyphosate applied as an herbicide equaled 1,151,051 kg on field corn, 1,544,954 kg on soybeans, 65,230 kg on wheat, 34,573 kg on oats and mixed grains, 11,542 kg on white beans, 27,980 kg on hay and pasture, and 24,144 kg on other field crops (OMAFRA 2015).

5.4 ENVIRONMENTAL FATE

The environmental fate of glyphosate, which includes the transport, partitioning, and transformation of this substance, is controlled by various physicochemical properties, degradation, and other loss processes. Glyphosate is a non-volatile, highly polar, non-residual herbicide that has low potential for environmental persistence and is unlikely to bioaccumulate; the chemical is either degraded or inactivated by adsorption to soil (Smith and Oehme 1992). Microbial degradation in soils and water is an important fate process; reported half-lives range from 2 to 215 days in soils and from 1.5 to 130 days in waters (Battaglin et al. 2014; IPCS 1994; PAN 2009; Rueppel et al. 1977). The wide range of half-lives is a result of environmental conditions such as soil characteristics, pH, and endogenous microbial populations, which are factors that influence the rate of degradation. Glyphosate is not expected to be susceptible to hydrolysis; photodegradation has not been confirmed as an important fate process in any environmental media (Smith and Oehme 1992).

5.4.1 Transport and Partitioning

Glyphosate is not expected to change ionic form at pH levels of 5–8 and is expected to exist in its anionic form under most environmental conditions.

Air. Glyphosate has a low vapor pressure and is expected to exist in the particulate phase in the ambient atmosphere. There is potential for spray drift after application of herbicides, the extent of which is dependent on the mode of application. Aerial applications may result in considerable transport depending on climate conditions (IPCS 1994; Yates et al. 1978). Drift analysis has shown that 10–37% of applied herbicide can drift to non-target plants. Seedling and plant fatalities were found 20–100 m downwind after application, and residues have been detected at 400 and 800 m downwind following ground and aerial applications, respectively (PAN 2009). Photolysis in air is not an important fate process (Rueppel et al. 1977). Particulate-phase glyphosate can be removed from the atmosphere by wet or dry deposition.

Wet deposition of glyphosate and AMPA from the atmosphere ranged from 3.9 to 16 $\mu g/m^2$ and from 1.7 to 5.2 $\mu g/m^2$, respectively, as reported in a study conducted in Pace, Mississippi, and Blairsburg, Iowa in 2007 and 2008 (Chang et al. 2011). In a study conducted in 2001, the total annual deposition for glyphosate was reported as 49,000 ng/m^2 and the maximum concentration detected was 6,200 ng/L. The total annual deposition for AMPA was reported as 12,757 ng/m^2 and the maximum concentration detected was 1,200 ng/L. The majority of glyphosate detections occurred during the spraying season. Deposition rates and concentrations of glyphosate were higher at the urban sites; this was attributed to its non-agricultural uses. The highest deposition for glyphosate was detected when direct application of herbicide occurred in August 2001 and decreased more than 90% over the next several days, decreasing to residual concentrations by the end of November 2001. During this time, when precipitation occurred, levels of glyphosate were above the standard for drinking water in six out of eight water samples (Quaghebeur et al. 2004).

Water. Depending on its application, glyphosate may enter aquatic environments through direct application or as a result of overspray in areas near aquatic environments. There is evidence of limited run-off and leaching with sandy soils and heavy rainfall (Borggaard and Gimsing 2008). Partitioning into aqueous environments is attenuated by adsorption to soils and sediments.

Sediment and Soil. Glyphosate will have strong adsorption to most soils due to its ionic nature and is expected to bind to positively charged metal surfaces present in clay and soils. Adsorption occurs through hydrogen bonding ion exchange or complexes of the phosphonate anion as well as the ammonium cation with minerals present in soils (Miles and Moye 1988). In an unpublished report by Monsanto in 1978, <0.1–6.6% of applied activity was recovered in the solution that washed off of the soil columns under leaching conditions simulating a heavy rainfall (IPCS 1994). The potential for run-off and leaching ability of glyphosate was examined by Rueppel et al. (1977) in three soils. Using inclined soil beds and artificial rainfall scenarios, a maximum runoff off $<2x10^{-4}$ kg/ha was reported. Using thin layer chromatography and beta camera analysis, 97–100% adsorption to all three soils indicated that there is minimal possibility for leaching into groundwater. Although glyphosate is expected to adsorb strongly to soil particles and clay minerals, desorption may occur under certain conditions. It has been demonstrated that sorption decreases with increasing soil pH, increasing concentrations of inorganic soil phosphate, and decreasing mineral concentrations (Glass 1987; Gerritse et al. 1996; Piccola et al. 1994; Plimmer et al. 2004; Smith and Oehme 1992; Sprankle 1975). However, because of the strong sorption to most soils, mobility and the potential for migration into groundwater are low. The major degradation product, AMPA (CASRN 1066-51-9), also binds to soils and may be more mobile than glyphosate (Duke and Powles 2008; IPCS 1994). Leaching of glyphosate may be possible under certain environmental conditions; however, it is not expected to leach into groundwater under most environmental conditions.

Other Media. Glyphosate is not taken up from the soil by a plant's root system. After surface application of glyphosate, it may move from the point of application, typically the leaves, to other parts of the plant. Glyphosate can be absorbed into the plant or vegetable through its outer wall or skin and can move throughout the stem and leaves of the entire plant. Metabolism of glyphosate within the plant occurs slowly (Doublet et al. 2009; Smith and Oehme 1992; WHO 2005). Glyphosate is mobile inside the plant and may be transported within the phloem system into other tissues before the plant is killed (Duke and Powles 2008; Pankey 2000; Plimmer et al. 2004). Boerboom and Wyse (1988) investigated absorption and translocation of glyphosate using Canada thistle seeds with various concentrations of a formulation of glyphosate (356 g/L) and the surfactant POEA (178 g/L). Translocation from the treated leaf to the root was clearly observed. Translocation generally decreased as the concentration of glyphosate increased. Application of the smaller droplets resulted in greater translocation to the roots compared to application of larger droplets.

5.4.2 Transformation and Degradation

Glyphosate is readily and completely degraded in the environment mainly by microbial processes. Modes of degradation involving glyphosate oxidoreductase (GOX) and C-Plyase enzymatic pathways have been suggested. AMPA has been identified as the major metabolite in both soils and water. Sarcosine is an additional degradation product produced by the C-Plyase enzymatic pathway. Glyoxylic acid (CASRN 298-12-4) is an additional degradation product by the GOX enzymatic pathway. Both pathways result in complete mineralization to inorganic phosphate, carbon dioxide, ammonium, and water (Balthazor and Hallas 1986; Kishore and Jacob 1987; Shinabarger and Braymer 1986). AMPA has reported soil half-lives ranging from 60 to 240 days and aquatic half-lives similar to glyphosate (Battaglin 2014).

The high water solubility, low log K_{ow}, and ionic nature of glyphosate suggest that this compound would not be expected to bioaccumulate in aquatic organisms (IPCS 1994; WHO 2005). Jackson et al. (2009) measured whole-body bioconcentration factor (BCF) values for glyphosate in bluegill fish (*Lepomis macrochirus*) using EPA guideline method OPPTS 850.1730 for an exposure period of 28 days. A BCF value of 0.52 (log BCF -0.284) was reported, suggesting that bioconcentration was low. Accumulated residues of glyphosate in fish, crustaceans, and mollusks exposed to water containing glyphosate declined approximately 50–90% over 14–28 days after removal from the glyphosate water into glyphosate-free water (WHO 2005). Bioaccumulation of glyphosate in blackworms (*Lumbriculus variegatus*), following soil application of glyphosate and a commercial formulation, was investigated (Contardo-Jara et al. 2009). BCF values after 4 days of exposure to concentrations of 0.05–5 mg/L of both 98% pure glyphosate and the formulation Roundup Ultra (containing 360 g/L glyphosate isopropylamine salt) were measured at 20°C (Contardo-Jara et al. 2009). BCF values based on the fresh weight of the worms ranged from 1.2 to 5.9; the BCF values for pure glyphosate at 0.05, 0.5, and 5.0 mg/L were approximately 2.9, 1.1, and 2.8, respectively and BCF values for Roundup Ultra at 0.05, 0.5, and 5.0 mg/L were approximately 5.9, 3.8, and 2.7, respectively. The greater uptake of glyphosate from the Roundup Ultra sample was attributed to the surfactant in the formulation, POEA.

The mechanism of action for glyphosate's herbicidal properties involves the inhibition of enzymes in the shikimate pathway. Specifically, the enzyme enolpyruvylshikimate-3-phosphate synthase is inhibited, creating a deficiency of enolpyruvylshikimate-3-phosphate and an abundance of shikimate. It has been suggested that the actual death of the plant is due to the disruption of plant processes regulated by the shikimate pathway essential to plant health and growth such as the primary biosynthesis of aromatic amino acids like phenylalanine, tryptophan, and tyrosine, as well as lignin and chlorophyll, and secondary

processes such as flavonoid synthesis. These primary processes are exclusive to plants and some microorganisms and do not occur in any animals; therefore, the inhibition of enzyme production induced by glyphosate only affects species in the plant kingdom. It has also been suggested that the increased carbon flow to the shikimate pathway decreases carbon available for other essential photosynthetic processes (Muller and Applebyke 2010; Pankey 2000; Plimmer et al. 2004; Servaites et al. 1987).

In transgenic plants, glyphosate is converted to N-acetylglyphosate (CASRN 129660-96-4), a chemical that lacks herbicidal properties. This chemical may be further metabolized to N-acetyl (aminomethyl) phosphonic acid (N-acetyl-AMPA) (PAN 2009; Pioneer 2006).

Air. Glyphosate has low vapor pressure and is considered stable in ambient air. Photolysis in air was examined by Rueppel at al. (1977). Loss of ^{14}C-labelled glyphosate was <3% after 48 hours; therefore, direct photolysis is not an important fate process (48 hours of direct irradiation is similar to 16 8-hour days of sunlight).

Water. Glyphosate has high water solubility and is expected to exist as an anion at neutral pH (IPCS 1994; O'Neil et al. 2013). Based on experimental adsorption coefficients ranging from 8 to 377 dm^3/kg for various soil and clay substrates, glyphosate is expected to adsorb to suspended solids and sediments in water. Precipitation from water has been suggested due to water-insoluble metal complexes with iron(III), copper(II), calcium, and magnesium that have been found; coordination occurs through the amine nitrogen, the carboxylic oxygen, and the phosphate oxygen (Subramaniam and Hoggard 1988). Photodegradation in water is not expected to be an important fate process for glyphosate under environmentally relevant conditions. Experimental half-lives of <28 days upon exposure to natural light at pH 5, 7, and 9 have been reported (IPCS 1994; Rueppel et al. 1977). No detectable photodegradation was observed in a study using sterile water and exposure to ultraviolet (UV) light or natural sunlight (Smith and Oehme 1992). Lund-Hoje and Friestad (1986) exposed glyphosate to UV light at 254 nm at 20°C in the laboratory and exposed 1% glyphosate solutions in deionized water, polluted water, and water with suspended sediments to natural sunlight (measured λ=295–385 nm) outside at temperatures ranging from 20 to -5°C. Results indicated that photodegradation occurred faster in pure water as opposed to polluted water or water with sediments in which adsorption accounted for the majority of dissipated glyphosate. A photolytic half-life of 3–4 weeks was observed for glyphosate, at an initial concentration of 2,000 ppm in the deionized water exposed to UV light. A photolytic half-life of 5 weeks at 100 ppm was observed for glyphosate in deionized water, exposed to natural sunlight. The rate of hydrolysis is considered very slow. In a study at 35°C, glyphosate did not undergo hydrolysis in buffered solutions

with a pH of 5, 7, or 9. Laboratory studies have reported a half-lives of >14 days in water and sediment under aerobic conditions and 14–22 days under anaerobic conditions for glyphosate (IPCS 1994). In an aqueous hydrolysis study at 25°C in buffered solutions of pH 5, 7, and 9, glyphosate was considered hydrolytically stable, with extrapolated half-lives beyond 3 years (EPA Undated)

Rapid dissipation of glyphosate in small forest ponds was observed as a result of sediment sorption and microbial degradation (Goldsborough and Beck 1989). Dissipation in three ponds, pH 5.0–7.7, resulted in half-lives of 1.5–3.5 days. After 38 days, glyphosate was not detected in any of the samples. AMPA concentrations were consistently low throughout the study.

Microbial degradation of glyphosate in water sediments has been investigated. AMPA has been identified as the major metabolite in water. Rueppel at al. (1977) performed non-sterile and sterile soil/water shake flask experiments to examine the degradation of glyphosate under aerobic and anaerobic conditions. The ^{14}C-labeled glyphosate samples used were between 94.8 and 98.1% pure. Ray silt loam, Norfolk sandy loam, and Drummer silty clay loam soil samples were used. In the sterile soil test, 1.0% degradation was achieved after 7 days; the report suggests that abiotic chemical degradation is not a likely fate process for glyphosate. In the non-sterile aerobic and anaerobic tests in Ray silt loam, carbon labeled glyphosate achieved 46.8–55.3 and 33.5–55.3% degradation, respectively, after 28 days, measured by applied ^{14}C as CO_2 evolution. In the non-sterile aerobic tests in Drummer loams, both fresh and bin-stored, carbon-labeled glyphosate achieved just over 40% and just under 20% degradation, respectively, after 28 days, measured by applied ^{14}C as CO_2 evolution. In the fresh Drummer loam and Ray loam samples, no lag phases were observed and the bulk of the degradation occurred by day 7, after which time, the rate of degradation declined. The slowing of degradation was attributed to adsorption to soil. In Ray silt loam and Drummer silty clay loam, dissipation of glyphosate reached 90% after 14 and 80 days, respectively, and half-lives were reported as 3 and 25–27 days, respectively. The results were similar at different concentrations of glyphosate. In the non-sterile aerobic test in Norfolk sandy loam, carbon-labeled glyphosate achieved <10% degradation after 28 days, measured by applied ^{14}C as CO_2 evolution, and 43% dissipation occurred after 112 days. A half-life of 130 days was reported for Norfolk soil. The principle degradation product identified, AMPA, was confirmed in soil samples by nuclear magnetic resonance (NMR) imaging, mass spectral analysis, ion-exchange chromatography, and thin-layer chromatography. Minor degradation products identified included N-methylaminomethylphosphonic acid, glycine, N,N-dimethylaminomethylphosphonic acid, and hydroxymethylphosphonic acid, all of which were typically present at <1% (Rueppel et al. 1977). The metabolite, AMPA, achieved 16.1 and 34.8%

degradation after 63 days in Drummer and Ray loams, respectively, measured by applied ^{14}C as CO_2 evolution.

Abiotic degradation was examined by Ascolani Yael et al. (2014) in aqueous solution in the presence of copper salts; results indicated that glyphosate interactions with metal ions in soils may catalyze degradation to AMPA. Further investigation was proposed.

Sediment and Soil. Glyphosate is readily degraded in the terrestrial environment by a variety of microorganisms. Bacteria, actinomycetes, fungi, and other soil microbes have the ability to degrade glyphosate. AMPA has been identified as the major metabolite in soil. Glyphosate may also be degraded in soil to sarcosine and inorganic phosphate. Photodegradation is not expected to be an important fate process in soil.

After application of about 2.0 kg/ha active ingredient Roundup to Carnation Creek watershed (10 km^2 study area), 50% of the glyphosate residues in soil dissipated after 45–60 days and 82–94% dissipated after 360 days (Feng et al. 1990a).

It has been demonstrated that inorganic phosphate present in soils may inhibit some microbial degradation of glyphosate (Kishore and Jacob 1987). Strains capable of using glyphosate as a sole carbon, nitrogen, or phosphorus source, thereby degrading glyphosate, include *Flavobacterium* sp. (Balthazor and Hallas 1986), which is known to degrade glyphosate in the presence of phosphate, *Pseudomonas* sp. PG2982 (Kishore and Jacob 1987; Shinabarger and Braymer 1986), *Arthrobacter atrocyaneus* (Pipke and Amrhein 1988), and *Rhizobium* spp. (Liu et al. 1991). Biodegradation may involve co-metabolism with other energy sources as well (Sprankle et al. 1975). Degradation products include AMPA and glyoxylic acid, which are subsequently degraded to inorganic phosphate, carbon dioxide, and ammonium. In addition, some bacterial degradation results in the production of sarcosine and inorganic phosphate (Borggaard and Gimsing 2008; Kishore and Jacob 1987; Liu t al 1991; Pipke and Amrhein 1988; Shinabarger and Braymer 1986).

Microbial degradation of bound and unbound glyphosate in several soils resulted in 17.4–45% ultimate degradation after 28 days; the highest degradation rate was observed in Conover sandy clay loam soil (Sprankle et al. 1975). The majority of the degradation was attributed to co-metabolic processes of soil microbes, with possible chemical degradation occurring.

In a biodegradation experiment with activated sludge, the bacterial strain, *Flavobacterium* sp., was identified as the microorganism metabolizing glyphosate to AMPA. This degradation was followed by complete mineralization of AMPA, using the enzyme phosphonatase, to carbon dioxide (CO_2), phosphate (PO_4^{3-}), ammonium (NH^{4+}), and water (H_2O) (Balthazor and Hallas 1986).

A variety of microorganisms are capable of degrading glyphosate. In one degradation pathway, the initial step involves cleavage of the carbon-phosphate bond to produce sarcosine and inorganic phosphate. This is followed by conversion of sarcosine to glycine and formaldehyde. *Pseudomonas* sp. PG2982 uses the enzyme, C-P lyase, to cleave the carbon-phosphate bond in glyphosate, producing sarcosine. This is followed by the cleavage of sarcosine into glycine and formaldehyde (Kishore and Jacob 1987; Shinabarger and Braymer 1986). Glycine and formaldehyde are metabolized in other biosynthesis processes, such as the oxidation of formaldehyde to carbon dioxide. Multiple strains in the bacterial family *Rhizobiaceae* have the ability to metabolize glyphosate. Liu et al. (1991) found that rhizobia bacterial cells took up close to 85% of available glyphosate within 30 minutes, after which time, the percentage began to decrease. Thin layer chromatography confirmed the presence of sarcosine and glycine as degradation products.

Doublet et al. (2009) studied the degradation of plant absorbed glyphosate in soils. Plants containing residues of glyphosate can enter the soils during crop cycling or harvesting. Degradation of glyphosate was different depending on the plant tissue in which it was absorbed. Mineralization rate constants (k (day^{-1})) ranged from 0.031 to 0.097 in the apex of oilseed rape and in the lamina of maize, respectively. It was noted that absorption of glyphosate in plants delayed degradation in soil.

Glyphosate is expected to adsorb strongly to soil particles and clay minerals; however, the amount of glyphosate sorbed decreases with increasing soil pH. Adsorption and desorption of glyphosate were examined using HPLC (Gerritse et al. 1996; Glass 1987; Piccola et al. 1994; Sprankle et al. 1975). Adsorption to agricultural soils and clay minerals and the effects of pH and cation saturation were examined by Glass (1987). The K_{oc} values were 4,900 for clay loam with pH 7.5 and organic content (OC) of 1.56%; 3,400 for silt loam with pH 5.8 and OC of 1.64%; and 2,600 for sandy loam with pH 5.6 and OC of 1.24%. The adsorption and desorption of glyphosate and the effects of soil characteristics in four various soil types were assessed (Piccolo et al. 1994). Some characteristics for the four soils follow: Sample A, pH 8.0 and 0.00 OC % (64.1% silt); sample B, pH 5.8 and 3.73 OC% (46.3% sand); sample C, pH 4.6 and 9.23 OC % (81.5% sand); and sample D, pH 8.3 and 0.45 OC % (82.4% silt). The greatest adsorption occurred in the soil with the highest concentrations of iron (4.74%) and aluminum (1.57)

oxides (sample B); the greatest desorption occurred in the soil with lowest concentration of iron (0.18%) and aluminum (0.16%) oxides (sample A). The percent desorptions of glyphosate from the four soils were 81% in sample A, 15% in sample B, 72% in sample C, and 35% in sample D. A ligand exchange mechanism is hypothesized for the adsorption of glyphosate involving either the phosphonic component or the carboxylic component of this substance and adsorption to iron and aluminum sites (Benetoli et al. 2010; Piccola et al. 1994). The adsorption and desorption of both glyphosate and its metabolite, AMPA, were examined by Gerritse et al. (1996) using five soil types. K_{oc} values calculated for soil organic carbon ranged from 8.5 to $5x10^6$ after 1 day and from 45 to $>5x10^6$ after 1 week. The strongest adsorption occurred in the soil with the highest iron and aluminum content. The weakest adsorption occurred in the soil with the highest organic content. These results indicate that glyphosate has a notable affinity towards some soils, particularly with lower pH values and greater mineral content, and desorption occurs under certain environmental conditions especially as pH values increase and mineral concentrations decrease.

During a monitoring study with mixtures of Roundup plus an additional herbicide, soil adsorption and desorption studies were performed on soils from Baton Rouge, Bridge City, and Hammond Louisiana (LaDOTD 1995). The Hammond soil with a pH <8 adsorbed >90% of the applied glyphosate. Adsorption values (Kf) were 8.7, 0.1, and 0.34 for Baton Rouge, Bridge City, and Hammond soils, respectively. Desorption values (Kd) were 355, 0.04, and 0.005 µg/g for Baton Rouge, Bridge City, and Hammond soils, respectively.

Greater than 90% of the glyphosate residues detected in forest soil samples (pH 4.20–5.28), where herbicides containing glyphosate had been sprayed, were found in the upper layers (depth of 0–15 cm) of the soils in both seasonally flooded and well-drained soils, indicating minimal leaching of glyphosate (Feng et al. 1990b).

Glyphosate dissipates from soil under certain environmental conditions. Half-life values between 3 and 174 days have been reported. In field experiments, dissipation from the soil due to run-off has been demonstrated (IPCS 1994). Landry et al. (2005) examined the leaching potential and mineralization of glyphosate in vineyard soils by monitoring outdoor soil columns from May 2001 to May 2002. Bare and grass-covered soils with pH values ranging from 8.0 to 8.4 were studied. Sand, silt, and clay contents were 23.8–34.4, 36.5–39.6, and 29.1–36.9%, respectively, of the bare soils and 26.2–35.6, 34.2–41.3, and 29.6–32.5%, respectively, of grass-covered soils. An aqueous solution of herbicide containing 340 mg/L glyphosate was applied to both soil column surfaces. Effluents from the bare and grass-covered soils

were collected weekly and after heavy precipitation to evaluate leaching of glyphosate and AMPA. Glyphosate was detected in 37% of the bare soil leachates and 27% of the grass-covered soil leachates. The highest concentrations measured from the bare soil leachate and grass-covered leachate were 17 and 2.7 µg/L, respectively. AMPA was detected in 90% (maximum concentration 9.4 µg/L) of the bare soil leachates and 41% (maximum concentration 3.5 µg/L) of the grass-covered soil leachates. Mineralization analysis was performed at 20°C for 42 days in both soils. In the grass-covered soil and bare soil, ^{14}C-labeled glyphosate achieved 46.5 and 43.5% CO_2 evolution after 42 days, respectively. Rapid degradation was observed with no lag phase; the highest rate of degradation occurred within the first 2 days. It was suggested that the initial rapid degradation was based on the degradation of free glyphosate and slowing rates of degradation were attributed to the degradation of adsorbed glyphosate.

Other Media. After application of herbicides, 30–97% of the applied glyphosate may be taken up by the plant by absorption from the treated leaves. Roundup solutions, containing surfactants (and adjuvants), have a higher rate of absorption compared to glyphosate water solutions (Doublet et al. 2009). Surfactants in herbicide formulations aid in the adsorption of glyphosate. Glyphosate is absorbed by plant foliage and transported or moved through the plant via phloem vessels; translocation patterns depend on the specific species of plant. Glyphosate enters these vessels slowly, but once inside, it becomes 'trapped' because of the pH within the vessels, which causes ionization (Gomes et al. 2014; IPCS 1994). Glyphosate may be degraded or metabolized in plants, AMPA is a notable degradation product (Duke 2011). An examination of the metabolism of glyphosate in soybean and canola suggest that some plants use a GOX enzyme for the conversion of glyphosate to AMPA. Degradation of glyphosate in glyphosate-resistant crops may give a better picture of the metabolic processes without interferences found in conventional crops. In transgenic plants, glyphosate is converted to N-acetylglyphosate, which lacks herbicidal properties. This chemical may be further metabolized to N-acetyl-AMPA (PAN 2009; Pioneer 2006). Glyphosate and AMPA accumulate less in glyphosate-resistant crops than in conventional crops. Lower glyphosate and AMPA levels in transgenic canola compared to conventional soybean suggested that metabolism is more rapid in transgenic canola (Duke 2011).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to glyphosate depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of glyphosate in unpolluted atmospheres and in pristine surface waters are often so

low as to be near the limits of current analytical methods. In reviewing data on glyphosate levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-3 shows the lowest limits of detection (LODs) that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-4.

Table 5-3. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.01 ng/m^3	Chang et al. 2011
Drinking water	5.99 µg/L	EPA 1990
Surface water and groundwater	Glyphosate and AMPA 0.02–0.10 µg/L	Lee et al. 2002; USGS 2002
Ground, surface, and well water	0.05 µg/L	NEMI 2005
Soil and sediment	Organic soil =0.05 µg/g Mineral soil=0.02 µg/g Foliage=0.10 µg/g Sediment=0.03 µg/g	Thompson et al. 1989
Whole blood	15 ng/mL	Aris and LeBlanc 2011
Urine	0.09 ng/mL	Biagini et al. 2004
Crops and commodities	0.01 mg/L	Alferness 194

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

AMPA = aminomethylphosphonic acid

Table 5-4. Summary of Environmental Levels of Glyphosate

Media	Low	High	For more information
Outdoor air (ppbv)	<0.01 ng/m^3 glyphosate; <0.01 ng/m^3 AMPA	9.1 ng/m^3 glyphosate; 0.97 ng/m^3 AMPA	Table 5-5
Surface water (ppb)	0.02 µg/L	27.80 µg/L	Table 5-6
Ground water (ppb)	0.01 µg/L	2.2 µg/L	Table 5-7
Drinking water (ppb)	Not detected		
Food (ppb)	0.078 mg/kg	5.47 mg/kg	Section 5.5.4, Other Media
Sediment	Not detected		Table 5-8

AMPA = aminomethylphosphonic acid

A study by the USGS evaluated 3,732 environmental samples across 38 states from several studies examining glyphosate in the environment; the samples were collected between 2001 and 2010 from 1,341 different sites (Battaglin et al. 2014). Glyphosate was detected in 39.4% of all the samples, with a median value of <0.02 µg/L and a maximum value of 476 µg/kg. Its degradation product, AMPA, was detected in 55% of all the samples, with a median value of 0.04 µg/L and a maximum value of 397 µg/kg. Groundwater (n=1,171) had the smallest percentage of detections, with 5.8% for glyphosate and 14.3% for AMPA. Glyphosate was detected in 53% of the 1,508 stream samples and AMPA was detected in 72%. Glyphosate was detected in 34% and AMPA was detected in 30% of the 104 small body water samples such as lakes and ponds. Out of 11 waste water treatment plant (WWTP) samples, glyphosate and AMPA were detected in 9.1 and 82%, respectively. Out of 85 precipitation samples, glyphosate was detected in 71% and AMPA was detected in 72%. Glyphosate was detected in 71% of the 374 ditch and drain samples, with a median value of 0.02 µg/L and a maximum value of 427 µg/L. Glyphosate was only detected without its degradation product, AMPA, in 2.3% of all of the samples; AMPA was detected without glyphosate in 17.9% of the samples. In 42.7% of all of the samples, neither analyte was detected. Several sites with multiple samples during the years 2001–2005 and 2006–2010 indicated that the detection frequency and median concentration of both glyphosate and AMPA had increased in the environment (Battaglin et al. 2014). The highest level of glyphosate was detected in soils and sediments. Out of 45 samples, glyphosate was detected in 91%, with a median value of 9.6 µg/kg and a maximum value of 476 µg/kg. AMPA was detected in 93.3% of 45 samples, with a median value of 18 µg/kg and a maximum value of 341 µg/kg.

5.5.1 Air

Ambient air monitoring data for glyphosate are compiled in Table 5-5.

Table 5-5. Outdoor Air Monitoring Data for Glyphosate

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Mississippi, Iowa	Agricultural ambient air	2007–2008	<0.01–9.1 ng/m^3 glyphosate; <0.01–0.97 ng/m^3 AMPA	Median: 0.08–0.48 ng/m^3 glyphosate; 0.02–0.06 ng/m^3 AMPA	Glyphosate was detected in 61–100% of samples; AMPA in 56–86%	Chang et al. 2011
Baton Rouge, Bridge City,	Agricultural breathing zones	June 19, 1990–October 9, 1990	<0.1–138.6 µg/m^3		Breathing zone air Sampled in areas where mixtures of commercial	LaDOTD 1995

Table 5-5. Outdoor Air Monitoring Data for Glyphosate

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Hammond, Louisiana					herbicides using spray equipment with operating capabilities of 0.37 L/minute	

AMPA = aminomethylphosphonic acid

5.5.2 Water

Water monitoring data for glyphosate are compiled in Tables 5-6 and 5-7.

5.5.3 Sediment and Soil

Sediment and soil monitoring data for glyphosate are compiled in Table 5-8.

Table 5-6. Finished and Surface Water Monitoring Data for Glyphosate

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Kansas	Finished water	July 6, 2010	Not detected		EPA STORET data: Routine monitoring samples from USGS Kansas Water Science Center, MDL 0.02 µg/L.	WQP 2017
United States	Surface water	January to December 2016	0.02–5.1 µg/L	Mean: 0.30; Median 0.10 µg/L	EPA STORET data: Routine monitoring samples from USGS Science Centers in Arkansas, California, Colorado, Connecticut, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Michigan Center, Maryland, Massachusetts, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, North Dakota, Oregon, South Carolina, Texas, Utah, Washington, and Wyoming.	WQP 2017
United States	Surface water	January to December 2015	0.02–24.20 µg/L	Mean: 0.27; Median 0.08 µg/L	EPA STORET data: Routine monitoring samples from Minnesota Department of Agriculture–Pesticide and USGS Science Centers in Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Massachusetts, Michigan Center, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Dakota, North Washington, Ohio, Oklahoma, Oregon, South Carolina, South Dakota, Texas, Utah, Washington, and Wyoming.	WQP 2017

Table 5-6. Finished and Surface Water Monitoring Data for Glyphosate

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
United States	Surface water	January to December 2014	0.02–8.10 µg/L	Mean: 0.38; Median 0.10 µg/L	EPA STORET data: Routine monitoring samples from Minnesota Department of Agriculture–Pesticide and USGS Science Centers in Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, Texas, Utah, Virginia, Washington, and Wyoming.	WQP 2017
United States	Surface water	March to October 2013	0.02–27.80 µg/L	Mean: 0.85; Median 0.34 µg/L	EPA STORET data: Routine monitoring samples from Minnesota Department of Agriculture and USGS Science Centers in , Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Minnesota, Missouri, Nebraska, New York, North Carolina, Ohio, South Dakota, Wisconsin, and Wyoming.	WQP 2017
Southern Ontario	Rivers, small streams, agricultural ditches, and low-flow wetlands	May and mid-December 2004; April and November 2005	5–41 µg/L		2004: 203 surface water samples were collected from 26 sites; 2005: 299 samples were taken from 58 sites. Approximately 50% of the sites detected glyphosate multiple times; AMPA was detected at trace levels between 20 and 66 µg/L in 5.4% of samples.	Struger et al. 2008

Table 5-6. Finished and Surface Water Monitoring Data for Glyphosate

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Minnesota, Wisconsin, Nebraska, Iowa, Illinois, Indiana, Ohio, Kansas, and Missouri	Streams	2002	Minimum of 0.10–0.46 µg/L detected in Iowa, Missouri, and Wisconsin; Maximum of 0.54–8.7 µg/L detected in Illinois, Indiana, Kansas, Minnesota, Nebraska, and Wisconsin		51 locations; samples collected after the application of pre-emergence herbicides, after the application of post-emergence herbicides, and during the harvest season. Glyphosate was detected at levels above the method reporting limit of 0.10 µg/L in 35% of the pre-emergence samples, in 40% of the post-emergence samples, and in 31% of the harvest season samples. AMPA was detected at levels >0.10 µg/L in 53% of the pre-emergence samples, in 83% of the post-emergence samples, and in 73% of the harvest season samples.	Battaglin et al. 2005
Mississippi, Iowa, Indiana	Rainwater	2004, 2007–2008	<0.01–2.5 µg/L glyphosate; <0.01–0.48 µg/L AMPA	Median: 0.1–0.2 µg/L glyphosate; <0.01–0.1 µg/L AMPA	Glyphosate was detected in 63–92% of samples; AMPA was detected in 36–92% of samples.	Chang et al. 2011
Flanders, Belgium	Rainwater	2001	Max during spraying season: 6,200 ng/L Glyphosate; 1,200 ng/L AMPA	Average annual concentrations: 78 ng/L glyphosate and 20 ng/L AMPA	Glyphosate detected in 10% of samples, AMPA was detected in 13% of samples.	Quaghebeur et al. 2004

AMPA = aminomethylphosphonic acid; EPA = U.S. Environmental Protection Agency; MDL = method detection limit; STORET = STOrage and RETrieval; USGS = U.S. Geological Survey

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Table 5-7. Groundwater Monitoring Data for Glyphosate

Location(s)	Geographic type	Date(s)	Range	Notes	Reference
Wyoming	Groundwater	September 9, 2010	1.6 µg/L	EPA STORET data: Routine monitoring sample from USGS Wyoming Water Science Center	WQP 2017
Florida	Groundwater	March 2, 2010	0.14 µg/L	EPA STORET data: Routine monitoring sample from USGS Florida Water Science Center	WQP 2017
Louisiana	Groundwater	April, October, and November 2011	0.03–2.2 µg/L	EPA STORET data: Routine monitoring sample from USGS Louisiana Water Science Center; depths 43.5–82 feet	WQP 2017
Alabama, Texas	Groundwater	February and April, 2012	0.01–0.06 µg/L	EPA STORET data: Routine monitoring sample from USGS Alabama Water Science Center; USGS Texas Water Science Center	WQP 2017
Kansas	Groundwater	June and August 2014, June 2015, July 2016	0.02–0.24 µg/L	EPA STORET data: Routine monitoring sample from USGS Kansas Water Science Center	WQP 2017
Minnesota	Well water	October and November 2014, 2015	Not detected	EPA STORET data: Routine monitoring sample from Minnesota Department of Agriculture Pesticide Monitoring Program; activity depth reported at 0 m	WQP 2017
38 U.S. states and the District of Columbia	Groundwater	2001–2010	Median=<0.02 µg/L; maximum=2.03 µg/L	Detected in 68 out of 1,171 samples	Battaglin et al. 2014

EPA = U.S. Environmental Protection Agency; STORET = STOrage and RETrieval; USGS = U.S. Geological Survey

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Table 5-8. Sediment and Soil Monitoring Data for Glyphosate

Location(s)	Geographic type	Date(s)	Range	Notes	Reference
Big Valley Rancheria, California	Sediment	July 6, 2010	Not detected	EPA STORET data: Routine monitoring samples from Big Valley Band of Pomo Indians of the Big Valley Rancheria, California: two samples; depth: 0.152 m; MDL: 0.017 mg/kg	WQP 2017
38 U.S. states and the District of Columbia	Soil and sediment	2001–2010	Median: 9.6 µg/g; maximum: 476 µg/g	Detected in 41 out of 45 samples	Battaglin et al. 2014
Willapa Bay, Washington	Estuary	July 1997–1999	1997 mudflat samples: 2.58–16.3 µg/g; 1998 mudflat samples: 3.11–9.94 µg/g; 1999 mudflat samples: 0.311–1.21 µg/g; 1997 meadow samples: 0.090–0.265 µg/g; 1998 meadow samples: 0.163–2.30 µg/g; 1999 meadow samples 0.472–1.32 µg/g (dry weight)	An aqueous herbicide formulated with Rodeo (5% solution v/v) and LI-700 (2% solution) was applied in mudflat and cordgrass plots of land in 1997 and 1998	Kilbride and Paveglio 2001

EPA = U.S. Environmental Protection Agency; MDL = method detection limit; STORET = STOrage and RETrieval

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5.5.4 Other Media

In 2006, 20 prepared food samples were examined for glyphosate residues using electrospray ionization–liquid chromatography tandem mass spectrometry with limit of quantitation of 0.01 mg/kg and an LOD of 0.005 mg/kg (McQueen et al. 2012). Composite food samples assessed had a mean concentration of 0.08 mg/kg.

Four weeks after application, concentrations of glyphosate in corn, cotton, soybeans, and wheat grown in soil treated with 4.5 kg/ha glyphosate were 0.21, 0.26, 0.20, and 0.20 mg/kg, respectively. Six weeks after application, concentrations in corn, cotton, soybeans, and wheat were 0.14, 0.21, 0.29, and 0.18 mg/kg, respectively, and 8 weeks after application, concentrations in corn, cotton, soybeans, and wheat were 0.079, 0.42, 0.076, and 0.35 mg/kg, respectively (FAO 2005). Four-week concentrations of glyphosate in control crops of corn, cotton, soybeans, and wheat were 0.068, 0.04, 0.029, and 0.008 mg/kg, respectively. Six-week concentrations in control crops of corn, cotton, soybeans, and wheat were 0.089, 0.020, 0.11, and 0.015 mg/kg, respectively, and 8-week concentrations in control crops of corn, cotton, soybeans, and wheat were 0.022, 0.27, 0.045, and 0.061 mg/kg, respectively (FAO 2005)

Glyphosate concentrations found in edible food treated with formulations of the glyphosate herbicide, Roundup, ranged from undetectable, <0.05 mg/kg, in several foods like bananas to 20 mg/kg in barley and transient soya beans (FAO 2005). Genetically modified, or transient, and conventional food samples were studied. Herbicidal application techniques used on the food samples examined included pre-harvest application, directed ground spray, pre-emergence, and recirculating spray application methods. Application rates ranged from 0.36 to 7.7 kg/ha. The highest concentration found in banana pulp was 0.16 mg/kg. All kiwifruit assessed in the study had undetectable residues. Olives had residues ranging from undetectable to 12 mg/kg. Dry beans had residues ranging from undetectable to 10 mg/kg. Dry peas had residues ranging from undetectable to 8.9 mg/kg. Lentils had residues ranging from undetectable to 17 mg/kg. Transient sugar beet root had residues ranging from undetectable to 8.6 mg/kg. Conventional maize had residues ranging from undetectable to 3 mg/kg. Transient maize had residues ranging from undetectable to 0.83 mg/kg. Oats had residues ranging from undetectable to 19 mg/kg. Rye grain had residues ranging from 0.1 to 4.6 mg/kg. Wheat grain had residues ranging from 0.09 to 6.4 mg/kg. Sugarcane had residues ranging from undetectable to 15 mg/kg. Coffee and tea had levels ranging from undetectable to 9.6 mg/kg. Glyphosate residues in Kona Hawaiian coffee beans prior to roasting were 0.58 mg/kg, and the roasted beans had residues of 0.06 mg/kg.

Lettuce, carrots, and barley contained glyphosate residues up to 1 year after the soil was treated with 3.71 pounds of glyphosate; glyphosate was not included in compounds tested for by the Food and Drug Administration's (FDA) Pesticide Residue Monitoring Program (PRMP), nor in the United States Department of Agriculture's Pesticide Data Program (PDP) (FDA 2015; NPIC 2015).

A review by WHO reported that glyphosate was not detected in cereal grains at harvest when application of the herbicide occurred before planting (WHO 2005). Glyphosate was detected in cereals at mean residue levels of 0.2–4.8 mg/kg when application of the herbicide was prior to harvesting. In one assessment, levels of glyphosate were found to decrease upon processing grains to flour from 1.6 to 0.16 mg/kg (WHO 2005). In wheat treated with either Glyphos or Roundup herbicides, levels of glyphosate were also found to decrease upon processing grains to flour from 0.28–1.0 mg/kg in the grains to <0.05 mg/kg in the flour (FAO 2005). Glyphosate residues in oats stored at room temperature compared to frozen storage were similar, 3.5 and 3.1 mg/kg, respectively (FAO 2005) After exposure to glyphosate at 10 mg/L for 14 days, fish concentrations ranged from 0.2 to 0.7 mg/kg and decreased upon exposure to glyphosate-free water (WHO 2005).

A review by Williams et al. (2000) reported U.S. glyphosate residue data for wheat treated with maximum rates of Roundup. Wheat crop residues consisted of a mean glyphosate concentration of 0.69 μg/g (mg/kg), with a maximum concentration of 2.95 μg/g (mg/kg). Transient soybeans treated with maximum rates of Roundup showed a mean glyphosate concentration of 2.36 μg/g (mg/kg) and a maximum concentration of 5.47 μg/g (mg/kg).

Glyphosate was detected in carrot samples at average concentrations of 0.078±0.002 mg/kg and in spinach at 0.104±0.005 mg/kg (Zhao et al. 2011).

Glyphosate residues were examined on alder and salmonberry foliage and leaf litter sprayed with glyphosate at 2.0–2.1 kg/ha (Feng et al. 1990b). Foliar residues on alder and salmonberry were 261 and 448 ppm (dry weight), respectively, after the initial application of the herbicide. Leaf litter of alder and salmonberry collected 15 days post-application had glyphosate residues of 12.5 and 19.2 ppm (mg/kg), respectively. After 8–9 days, 50% dissipation was reported for the glyphosate residue. AMPA residues in the leaf litter decreased, and at 29 days after application of the herbicide, concentrations of AMPA were not detected.

5.6 GENERAL POPULATION EXPOSURE

The main routes of exposure to glyphosate for the general public result from the ingestion of crops with residues of glyphosate, and dermal, ocular, or inhalation exposure from direct application of herbicides containing glyphosate (EPA_2009c). Limited monitoring data indicate that oral exposure may occur from drinking contaminated well water supplied from groundwater contaminated with glyphosate; concentrations reported in groundwater are relatively low, and this chemical has low leaching potential. Upon dermal exposure, absorption through the skin is expected to be low based on dermal absorption studies, where an estimated 0.8–2.2% percutaneous absorption of glyphosate occurred in a study using ^{14}C-radiolabeled glyphosate in a Roundup formulation. Evidence has shown that proper hygiene removes glyphosate from skin and will deter absorption through the skin (Wester et al. 1991). Exposure may also occur via ingestion of food with herbicidal residues containing glyphosate as a result of its application. Human intake of glyphosate via food and water such as total diet studies are not available (NPIC 2015). The FDA has not performed a total diet study on glyphosate. Glyphosate has not been included in the FDAs Pesticide Residue Monitoring Program Reports for the fiscal years 2009 through 2014 (FDA 2013a, 2013b, 2014, 2015, 2016, 2017). Glyphosate is a non-volatile compound, and drift of herbicidal sprays may occur with aerial and ground equipment (Yates et al. 1978); therefore, some exposure via inhalation and possible ocular exposure may occur after spraying.

Occupational exposure may occur in both forestry and agricultural settings from the direct use of herbicides containing glyphosate. The most probable routes for occupational exposure are via inhalation and dermal contact with this chemical at workplaces where glyphosate or products containing this chemical are produced or used. Oral exposure may occur from accidental ingestion. Minimal data on occupational exposure indicate that exposure concentrations for workers applying glyphosate in certain herbicide formulations are low. During the years 1990–1993, exposure to glyphosate of field workers applying mixtures of Roundup plus an additional herbicide in areas of Louisiana was assessed (LaDOTD 1995). Mixtures of Roundup (active ingredient glyphosate) plus Garlon-3A (active ingredient triclopyr) and Roundup (active ingredient glyphosate) plus 2,4-D (active ingredient 2,4-dichlorophenoxyacetic acid) were applied by 13 workers using spray equipment with operating capabilities of 0.37 L/minute. Levels of glyphosate were detected in the workers urine using HPLC with a detection limit of 100 ppb. Levels ranging from non-detectable to 175 µg were reported for both working and non-working days. Urine concentrations were higher than concentrations found in the collected air samples of the breathing zone. It was noted that inhalation exposure was very low compared with threshold limits; the maximum air

concentration was 17.9 µg/m^3. Dermal contact and improper hygiene leading to ingestion of the herbicides were noted as the probable routes of exposure.

The Fourth National Report on Human Exposures to Environmental Chemicals, published and updated by the Centers for Disease Control and Prevention reporting biomonitoring data from the National Health and Nutrition Examination Survey (NHANES) for survey years 2005–2012, does not include data for glyphosate or its metabolite, AMPA (CDC 2017).

Farmers, with an average age of 45 years licensed as pesticide applicators in South Carolina and Minnesota, who applied herbicides containing glyphosate had average urine concentrations on the day of application of 3 µg/L (Acquavella et al. 2004). Lack of wearing rubber gloves was associated with higher concentrations in farmers' urine. Spouses, with an average age of 42.2 years residing with the farmers but having minimal or no involvement in the preparation or application of the herbicide, had relatively low and consistent urine concentrations, while children (ages 4–18 years) had an increase followed by a decrease in urine concentrations correlated with application (see Table 5-9). For the entire assessment period, 88–95% of all samples of children's urine were below the detection limit (1 µg/L [ppb] for a 100-mL urine sample). Farmers applying the pesticide had the highest concentrations. The highest concentration of glyphosate found in a child was from a teenage male (29 µg/L [ppb]) who had assisted with mixing and application of the herbicide.

Table 5-9. Human Monitoring Data

Medium		Concentrations/ minimum, maximum	Average	Notes	Reference
Tissue	Postmortem, approximately 12–13 hours after ingestion	Glyphosate (ppm): kidney 3,650; liver 600; blood; 550; brain; 100		After one individual ingested 200–250 mL Roundup with 72-91 g/mL glyphosate	Menkes et al. 1999
Urine	Pre-application	<1–15 µg/L (ppb)	Not reported	Farmers applying pesticide; average age: 45 years	Acquavella et al. 2004
	Day of pesticide application	<1–233 µg/L (ppb)	Geometric mean: 3.2 µg/L (ppb)		
	1-Day post-pesticide application	<1–126 µg/L (ppb)	Geometric Mean: 1.7 µg/L (ppb)		
	2-Day post-pesticide application	<1–81 µg/L (ppb)	Geometric mean: 1.1 µg/L (ppb)		

Table 5-9. Human Monitoring Data

Medium		Concentrations/ minimum, maximum	Average	Notes	Reference
	3-Day post-pesticide application	<1–68 µg/L (ppb)	Geometric mean: 1.0 µg/L (ppb)		
	Pre-application	<1–3 µg/L (ppb)	Not reported	Spouses not involved with application; average age: 42 years	
	Day of pesticide application	<1–2 µg/L (ppb)	Not reported		
	1–3-Day post-pesticide application	<1–1 µg/L (ppb)	Not reported		
	Pre-application	<1–17 µg/L (ppb)	Not reported	Children not involved with application; average age: 11.5 years	
	Day of pesticide application	<1–29 µg/L (ppb)	Not reported		
	1-Day post-pesticide application	<1–24 µg/L (ppb)	Not reported		
	2-Day post-pesticide application	<1–12 µg/L (ppb)	Not reported		
	3-Day post-pesticide application	<1–6 µg/L (ppb)	Not reported		
	Daily during 1-week working period	<0.1 ng/µL		Forest workers using pressurized herbicide sprayers; 8% Roundup (active ingredient 360 g/L isoproylamine salt)	Jauhiainen et al. 1991
	3 Weeks after 1-week working period	<0.1 ng/µL			
	Following mild to fatal ingestions of 20–500 mL pesticide	Glyphosate: 228 mg/L mild/moderate case; 22,300 mg/L fatal case; AMPA: 0.54 mg/L mild/moderate case; 91.5 mg/L fatal case		13 individuals ages 25–69 years	Zouaoui et al. 2013
Blood	Following mild to fatal ingestions of 20–500 mL pesticide	Glyphosate: 3.7 mg/L mild/moderate case; 6,640 mg/L fatal case; AMPA: 0.13 mg/L mild/moderate case; 15.4 mg/L fatal case			Zouaoui et al. 2013

AMPA = aminomethylphosphonic acid

Acquavella et al. (1999) evaluated 1,513 reported cases to the American Association of Poison Control Centers during the years 1993–1997 of ocular or dermal/ocular exposure to Roundup herbicides with glyphosate concentrations ranging from <2 to >20%. Of all exposure cases, 62% involved male subjects, >80% were in a residential setting, and about 15% were in occupational settings. During the time period, California and Texas had the greatest number of reported cases. Dilute Roundup formulations accounted

for about 82% of the exposures; 5% were with concentrated Roundup. Medical outcomes were similar for males and females; almost 17% had no effects attributed to the exposure and the majority (70%) had minor effects.

An estimated dermal and inhalation exposure value of about 8,000 µg/hour was reported from a study of workers employing spray applicators; this corresponds to an approximate exposure of 40 µg/kg body weight/day (8-hour working day for a 60-kg adult) (IPCS 1994).

Aris and LeBlanc (2011) examined blood concentrations of glyphosate in a group of 30 pregnant and 39 non-pregnant females residing in Sherbrooke, Canada. The study noted that none of the subjects worked or lived with an individual who worked with pesticides. Neither glyphosate nor AMPA were detected in the maternal or fetal cord serum of pregnant subjects. Additionally, AMPA was not detected in non-pregnant subjects. Glyphosate was detected in 5% of the non-pregnant subjects at a range of not detectable to 93.6 ng/mL, with a mean of 73.6 ng/mL (LOD=15 ng/mL).

As with the adult general population, the main route of glyphosate exposure for children is through ingestion and dermal contact. No data were located regarding glyphosate in breast milk; therefore, a determination of the importance of this route of child exposure has not been made. During the spring and summer of 2001, urinary pesticide concentrations were investigated in families residing in non-farm and farm households (Curwin et al. 2007a, 2007b). Concentration levels of atrazine and chlorpyrifos were notably higher in the farm families compared to the non-farm families; however, both metolachlor and glyphosate concentration levels were not very different between the non-farm and farm households. In addition, the concentrations of each pesticide were noticeably higher when the specific pesticide was applied at the farm, except for glyphosate; glyphosate concentrations did not differ greatly when comparing farms where the pesticide was used and where the pesticide was not used. Glyphosate was detected at concentration levels equal to or greater than the LOD (0.9 µg/L) in 66% of the 23 non-farm fathers, 75% of the 24 farm fathers, 65% of the 24 non-farm mothers, 67% of the farm mothers, 88% of the non-farm children, and 81% of the farm children. Glyphosate concentration levels in 17 children, living on a farm where the pesticide was applied ranged from 0.001 to 0.33 µg/kg/day, with 16% of the samples below the LOD. Concentration levels in eight children living on a farm where the pesticide was not applied ranged from 0.003 to 0.64 µg/kg/day, with 20% of the samples below the LOD.

McQueen et al. (2012) estimated glyphosate dietary exposure of 43 pregnant women at 0.001 mg/kg body weight/day. Results indicated that fetal exposure resulting from maternal exposure to glyphosate was minimal.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Farm-households, farm workers, and people employed in agricultural sectors will incur higher exposure to glyphosate, as agriculture is the largest industry for herbicide use. Field workers who apply herbicides containing glyphosate will likely incur higher exposures to this chemical. Levels of glyphosate in field workers urine has been shown to increase during spraying season; however, glyphosate levels did not appear to carry over from previous seasons (LaDOTD 1995).

Proper hygiene, such as adequate washing, will alleviate some potential for exposure to glyphosate. Protective clothing will also limit the potential for exposure. Products containing glyphosate that have accidentally been splashed, spilled, or sprayed onto skin surfaces should be wash thoroughly in a timely fashion. When applying or mixing herbicides, the operator should stand upwind to minimize inhalation.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of glyphosate is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of glyphosate.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

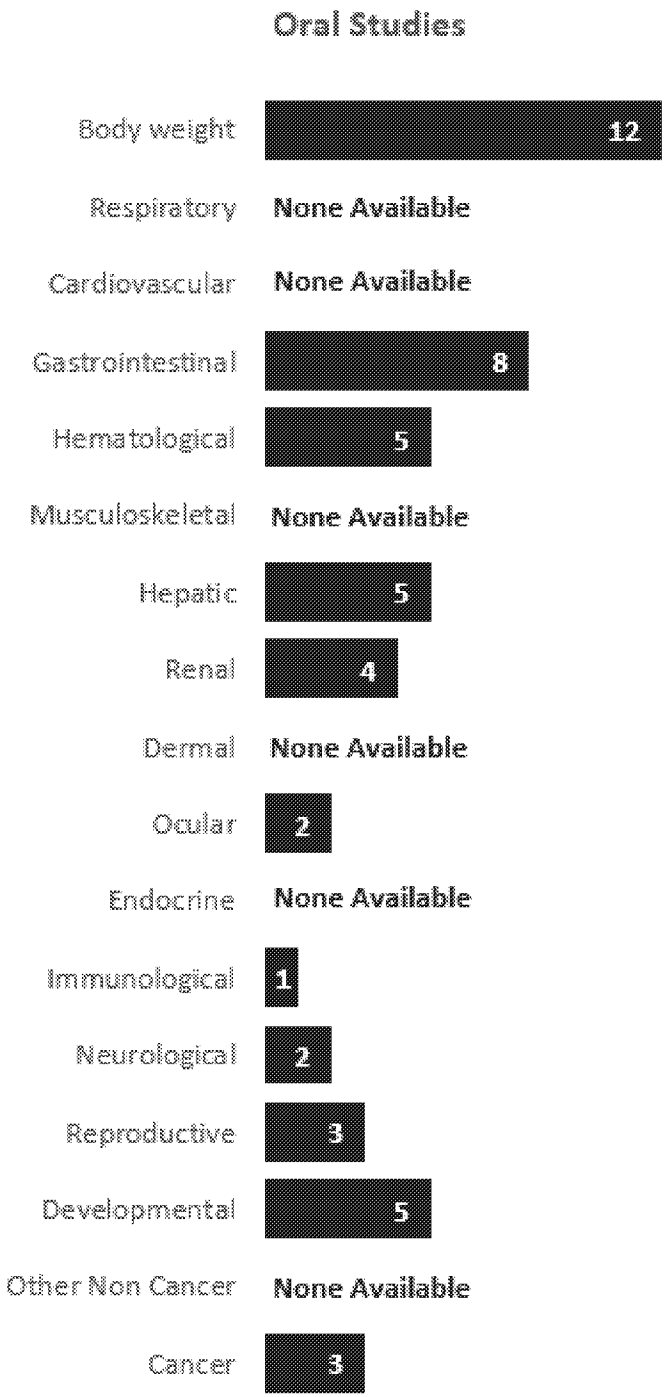
6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to glyphosate that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of glyphosate. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

The health effects of glyphosate have been evaluated in epidemiology and animal studies. Epidemiological studies are predominantly case-control and cohort epidemiology studies that examined possible associations between glyphosate exposure and selected health outcomes (noncancer and cancer endpoints), or case reports following accidental or intentional ingestion of glyphosate-containing products. These studies do not include data regarding the extent of the exposure or relative contribution of inhalation, oral and/or dermal exposure. They are of limited usefulness for human health risk assessment. Most reliable health effects data come from oral studies of animal examining potential body weight, gastrointestinal, hematological, hepatic, and developmental effects.

Figure 6-1. Summary of Existing Health Effects Studies of Animals Orally Exposed to Glyphosate Technical (Listed By Endpoint)*

Potential body weight, gastrointestinal, hematological, hepatic, and developmental effects of glyphosate technical effects were the most studied endpoints



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect.

6.2 Identification of Data Needs

Missing information in Figure 6-1 should not be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Oral studies in animals indicate that glyphosate toxicity is expressed only at oral dose levels many times higher than levels allowed as residues in food products. The general population is most likely to be exposed to glyphosate residues in food sources. Individuals can also be exposed to glyphosate during application of the herbicide or by being in the vicinity where it is applied. However, available dermal studies indicate that only 3–4% of dermally-applied glyphosate enters the blood. Data regarding the extent of absorption and potential health effects following inhalation exposure are lacking. Therefore, human and animal studies should be designed to evaluate airborne exposure levels and possible health effects from inhalation exposure.

Acute-, Intermediate-, and Chronic-Duration MRLs. As stated previously, most information is available from animal studies submitted to EPA's Office of Pesticides Programs using glyphosate technical (typically >90% purity) to fulfill requirements for the registration of a particular glyphosate formulation for use in the United States involve exposure to glyphosate technical (typically <90% purity). The general population will not be exposed to glyphosate technical, but rather to glyphosate formulations registered for use. Surfactants in glyphosate formulations are at least partly responsible for the toxic effects from overexposure to glyphosate formulations (Adam et al. 1997; Sawada et al. 1988; Williams et al. 2000). MRLs based on animal exposure to glyphosate technical would not adequately reflect human exposure to glyphosate formulations. MRLs for glyphosate formulations would need to be formulation specific due to the wide variation in glyphosate content and surfactants used in various glyphosate formulations and the fact that surfactants contribute to the toxicity of glyphosate formulations.

Health Effects

Respiratory. No publicly-available information was located regarding the effects of inhalation exposure in laboratory animals. Studies should be designed to evaluate respiratory effects in animals exposed to glyphosate by inhalation.

Developmental. Developmental toxicity studies in animal studies that employed oral exposure to glyphosate technical found no evidence of treatment-related effects at levels below the threshold of maternal toxicity. One study reported testicular lesions in weanling rats administered a glyphosate formulation orally at as little as 5 mg/kg/day. Additional studies should be designed to substantiate or refute this finding and to determine whether glyphosate or other ingredients in glyphosate formulations are involved in developmental effects on male reproductive organs.

Epidemiology and Human Dosimetry Studies. Limited information was located regarding respiratory effects associated with human exposure to glyphosate-based formulations. Additional studies should be designed to monitor exposure levels and health effects associated with individuals involved in the application of glyphosate-based products. There is limited evidence for glyphosate-related developmental effects in humans. Additional studies should be designed to evaluate possible associations between exposure to glyphosate and developmental endpoints in humans. Numerous agencies have evaluated glyphosate for possible associations between exposure and risk of various cancers. The majority of the human studies used self-reported ever/never glyphosate use as the biomarker of exposure. The results of these studies should be interpreted cautiously given the lack of monitoring data to quantify glyphosate exposure and the likely exposure to other pesticides. Most studies found no association between exposure to glyphosate-based products and risk of cancer. However, a possible association between exposure to glyphosate and risk of non-Hodgkin's lymphoma could not be ruled out, based on conflicting results. EPA (2016a) highlighted a need for mode of action data from mechanistic studies of glyphosate, additional epidemiology studies, and continued monitoring of the Agricultural Health Study cohort to further evaluate the potential carcinogenicity of glyphosate.

Biomarkers of Exposure and Effect. The most reliable biomarker of exposure to glyphosate is its detection in blood and urine. It is not likely that additional biomarkers of exposure to glyphosate would be more effective.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of glyphosate following oral and dermal exposure have been adequately described. Additional studies should be designed to evaluate the toxicokinetics of inhaled glyphosate.

Comparative Toxicokinetics. Significant species differences in the toxicokinetics of glyphosate are not likely.

Children's Susceptibility. Age-related differences in susceptibility to glyphosate have not been elucidated. Due to relatively large oral doses required to elicit adverse effects in glyphosate-exposed animals, it may be difficult to evaluate age-related differences in susceptibility.

Physical and Chemical Properties. The physical chemical properties of glyphosate are summarized in Chapter 4. No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. No information is available in the TRI database on facilities that manufacture or process glyphosate because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005). There is no information on releases of glyphosate from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005). Data on current manufacturing, processing, import/export values would be useful information. Data on current uses and disposal practices are outlined in Sections 5.2.3 and 5.2.4. Further studies on these practices do not appear to be essential.

Environmental Fate. Transport, partitioning, and bioconcentration data are available for glyphosate summarized in Section 5.4. In genetically modified plants, glyphosate is converted to N-acetyl-glyphosate; therefore, studies evaluating the possibility of additional crop and plant metabolites, along with the characteristic fates, may be beneficial (Pioneer 2006).

Bioavailability from Environmental Media. No data were identified that assess the bioavailability of glyphosate from environmental media such as soil and foods. Investigative studies on the relative bioavailability of glyphosate in different environmental media, especially food for human consumption, would add considerable value to the understanding of this chemical's behavior.

Food Chain Bioaccumulation. Studies are available that indicate that glyphosate has very low potential to bioconcentrate in aquatic organisms and is not expected to bioaccumulate in the food chain. Bioconcentration of glyphosate formulations may provide additional information.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of glyphosate in environmental media surrounding areas where these herbicides are applied would be useful information

to assess the potential risk of possible adverse health effects in populations living in the vicinity of these sites.

Exposure Levels in Humans. Studies are needed to investigate human intake of glyphosate via food and water, such as total diet studies.

Exposures of Children. Monitoring of children's exposure to glyphosate would be useful, in combination with children's health and susceptibility information, to assess the potential risk for deleterious effects.

Analytical Methods. Standardized methods that yield low detection limits for glyphosate and AMPA in biological samples (e.g., urine analysis, blood analysis) may provide more sensitivity and a more complete exposure analysis.

6.3 Ongoing Studies

Glyphosate is a potential candidate for addition to the California Environmental Contaminant Biomonitoring Program (CDPH 2013). Ongoing research identified in the National Institutes of Health (NIH) RePORTER (2017) database is summarized in Table 6-1.

Table 6-1. Ongoing Studies on Glyphosate

Investigator	Affiliation	Research description	Sponsor
De Roos, AJ	Drexel University	Occupational pesticide use and risk of lymphoid cancers	National Cancer Institute
Keating, AF	Iowa State University	Investigating modes of action of glyphosate-induced ovotoxicity	National Institute of Environmental Health Sciences

Source: RePORTER 2017

CHAPTER 7. REGULATIONS AND GUIDELINES

MRLs are substance specific estimates that are intended to serve as screening levels. They are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

No inhalation or oral MRLs were derived for glyphosate technical due to database inadequacies. No inhalation or oral MRLs were derived for glyphosate formulations due to variation in glyphosate content and surfactants used in various glyphosate formulations and the fact that surfactants contribute to the toxicity of glyphosate formulations.

The international and national regulations, advisories, and guidelines regarding glyphosate in air, water, and other media are summarized in Table 7-1.

Table 7-1. Regulations and Guidelines Applicable to Glyphosate

Agency	Description	Information	Reference
	Air		
EPA	RfC	Not evaluated	IRIS 1988
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2012e
	1-Day	20 mg/L	
	10-Day	20 mg/L	
	DWEL	70 mg/L	
	RfD	2.0 mg/kg/day	
	National primary drinking water regulations		EPA 2009c
	Maximum Contaminant Level	0.7 mg/L	
	Public Health Goal	0.7 mg/L	
	RfD	0.1 mg/kg/day[a]	IRIS 1989
WHO	Drinking water quality guidelines	Not established[b]	WHO 2017
FDA	EAFUS	No data[c]	FDA 2013c
	Cancer		
ACGIH	Carcinogenicity classification	No data	ACGIH 2016
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	Group D[d]	IRIS 1989
IARC	Carcinogenicity classification	Group 2A[e]	IARC 2017

Table 7-1. Regulations and Guidelines Applicable to Glyphosate

Agency	Description	Information	Reference
	Occupational		
ACGIH	TLV	No data	ACGIH 2016
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2016b 29 CFR 1910.1000, Table Z-1
	PEL (8-hour TWA) for shipyards and construction	No data	OSHA 2016c 29 CFR 1915.1000 Table Z
	PEL (8-hour TWA) for construction	No data	OSHA 2016a 29 CFR 1926.55 Appendix A
NIOSH	REL (up to 10-hour TWA)	No data	NIOSH 2016
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016c
AIHA	ERPGs	No data	AIHA 2015
DOE	PACs-air	No data	DOE 2016

[a]EPA's IRIS program has not planned to re-evaluate the RfD for glyphosate, which was based on increased incidence of renal tubular dilation in F3b offspring of rats receiving glyphosate from the diet at 30 mg/kg/day (EPA 1992g). EPA's Office of Pesticide Programs (EPA 2009a) noted that a subsequent similarly-designed 2-generation rat study (EPA 1992a) that employed doses up to 3,134 mg/kg/day found no evidence of treatment-related renal lesions in pups of either generation. Therefore, EPA (2009a) considered the finding in the F3b male pups from the 3-generation study to be a spurious result.
[b]Glyphosate and aminomethylphosphonic acid occur in drinking water at concentrations well below those of health concern, so a guideline value was not deemed necessary.
[c]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[d]Group D not classifiable as to human carcinogenicity. Note: EPA's IRIS program has not planned to re-evaluate the potential carcinogenicity of glyphosate. EPA's Office of Pesticide Programs (EPA 2016a) re-evaluated available human and animal data regarding the potential carcinogenicity of glyphosate and concluded that the strongest support is for the descriptor "*not likely to be carcinogenic to humans* at doses relevant to human risk assessment." However, EPA has not completed its Registration Review for Glyphosate.
[e]Group 2A: Probably carcinogenic to humans.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CFR = Code of Federal Regulations; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

Animal studies submitted to EPA's Office of Pesticides Programs to fulfill requirements for the registration of a particular glyphosate formulation for use in the United States involve exposure to glyphosate technical (typically <90% purity). Some animal studies in the open literature used glyphosate formulations that typically included 1–41% glyphosate technical (or glyphosate salts) and up to 18% surfactant (along with other "inert" ingredients). Surfactants in glyphosate formulations are at least partly responsible for the toxic effects from overexposure to glyphosate formulations (Adam et al. 1997; Sawada et al. 1988; Williams et al. 2000). The general population will not be exposed to glyphosate technical, but rather to glyphosate formulations registered for use. MRLs based on animal exposure to glyphosate technical would not adequately reflect human exposure to glyphosate formulations. Therefore, no MRLs were derived for glyphosate technical. No MRLs were derived for glyphosate formulations due to the wide variation in glyphosate content and surfactants used in various glyphosate formulations and the fact that surfactants contribute to the toxicity of glyphosate formulations.

APPENDIX B. LITERATURE REVIEW FRAMEWORK FOR GLYPHOSATE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to glyphosate.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for glyphosate. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of glyphosate have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of glyphosate are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects
    - Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The following main databases were searched in February 2015:

- PubMed
- National Library of Medicine's TOXLINE
- Scientist and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, and Medical Subject Headings (MeSH) terms for glyphosate. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance

priority list (SPL) resource page, and other items as needed. Regulations applicable to glyphosate were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
PubMed 2/18/2015	("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb])

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	("Roundup"[tw] AND (monsanto[tw] OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR "antifungal"[tw] OR "anti-fungal"[tw] OR "enzyme inhibitors"[Pharmacological Action] OR "enzyme inhibitors"[MeSH Terms] OR ("enzyme"[tw] AND inhibitor*[tw]) OR "enzyme inhibitors"[tw] OR "enzyme inhibitor"[tw] OR "herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[tw] OR "herbicide"[tw] OR "uncoupling agents"[Pharmacological Action] OR "uncoupling agents"[MeSH Terms] OR ("uncoupling"[tw] AND agent*[tw]) OR "uncoupling agent"[tw] OR "uncoupling agents"[tw] OR "pesticides"[mh] OR pesticide*[tw])) NOT (("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb]))

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	("34494-03-6"[tw] OR "MON 0459"[tw] OR "40465-66-5"[tw] OR "MON 14420"[tw] OR "MON 8750"[tw] OR "Roundup Hi-Load"[tw] OR "Roundup PRODry"[tw] OR "70393-85-0"[tw] OR "MON 8000"[tw] OR "Monsanto 8000"[tw] OR "Polado"[tw] OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])
	("39600-42-5"[tw] OR "Glyphosate potassium"[tw] OR "Glyphosate monopotassium salt"[tw] OR "Glyphosate potassium"[tw] OR "Glyphosate-potassium"[tw] OR "Monopotassium glyphosate"[tw] OR "Roundup Attack"[tw] OR "Roundup Energy"[tw] OR "Roundup Maxload"[tw] OR "Roundup Original Max"[tw] OR "Roundup Power Max"[tw] OR "Roundup Ultramax II"[tw] OR "Roundup Weathermax"[tw] OR "Touchdown Forte HiTech"[tw] OR "Transorb R"[tw] OR "Weathermax"[tw] OR "Zapp Qi"[tw] OR "70901-12-1"[tw] OR "Glyphosate-potassium"[tw] OR "Potassium glyphosate"[tw] OR "Potassium N-(phosphonomethyl)glycine"[tw] OR "Uragan Forte"[tw] OR "VisionMAX"[tw] OR "N-(phosphonomethyl)glycine potassium salt"[tw] OR "114370-14-8"[tw] OR "Glyphosate ammonium"[tw] OR "N-(phosphonomethyl)glycine ammonium salt"[tw] OR "69254-40-6"[tw] OR "Glyphosate-diammonium"[tw] OR "Diammonium N-(phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)glycine diammonium salt"[tw]) NOT (("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb]) OR ("Roundup"[tw] AND (monsanto[tw] OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR "antifungal"[tw] OR "anti-fungal"[tw] OR "enzyme inhibitors"[Pharmacological Action] OR "enzyme inhibitors"[MeSH Terms] OR ("enzyme"[tw] AND inhibitor*[tw]) OR "enzyme inhibitors"[tw] OR "enzyme inhibitor"[tw] OR "herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[tw] OR "herbicide"[tw] OR "uncoupling agents"[Pharmacological Action] OR "uncoupling agents"[MeSH Terms] OR ("uncoupling"[tw] AND agent*[tw]) OR "uncoupling agent"[tw] OR "uncoupling agents"[tw] OR "pesticides"[mh] OR pesticide*[tw]))) ((("glyphosate, isopropyl amine salt"[nm]) OR ("N-(phosphonomethyl)glycine trimethylsulfonium salt"[nm])) NOT (("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR

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Database search date	Query string
	"Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb]) OR ("Roundup"[tw] AND (monsanto[tw] OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR "antifungal"[tw] OR "anti-fungal"[tw] OR "enzyme inhibitors"[Pharmacological Action] OR "enzyme inhibitors"[MeSH Terms] OR ("enzyme"[tw] AND inhibitor*[tw]) OR "enzyme inhibitors"[tw] OR "enzyme inhibitor"[tw] OR "herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[tw] OR "herbicide"[tw] OR "uncoupling agents"[Pharmacological Action] OR "uncoupling agents"[MeSH Terms] OR ("uncoupling"[tw] AND agent*[tw]) OR "uncoupling agent"[tw] OR "uncoupling agents"[tw] OR "pesticides"[mh] OR pesticide*[tw]))))) OR (("38641-94-0"[tw] OR "Glyphosate-isopropylammonium"[tw] OR "Glyphosate isopropylamine salt"[tw] OR "Azural AT"[tw] OR "CP 70139"[tw] OR "Fosulen"[tw] OR "Glifosato estrella"[tw] OR "Glycel"[tw] OR "Glycine, N-(phosphonomethyl)-, cmpd with 2-propanamine (1:1)"[tw] OR "Glyfos AU"[tw] OR "Glyfos BIO"[tw] OR "Glyphosate isopropylamine salt"[tw] OR "Glyphosate mono(isopropylamine) salt"[tw] OR "Glyphosate-isopropylammonium"[tw] OR "Glyphosate-mono(isopropylammonium)"[tw] OR "Landmaster"[tw] OR "MON 139"[tw] OR "MON 39"[tw] OR "N-(Phosphonomethyl)glycine isopropylamine salt"[tw] OR "N-(Phosphonomethyl)glycine isopropylammonium salt"[tw] OR "N-(Phosphonomethyl)glycine monoisopropylamine salt"[tw] OR "Nitosorg"[tw] OR "Ron-do"[tw] OR "Utal"[tw] OR "Utal (herbicide)"[tw] OR "Vision (herbicide)"[tw] OR "2-Propanamine, compd, with N-(phosphonomethyl)glycine (1:1)"[tw] OR "Glycine, N-(phosphonomethyl)-, compd. with 2-propanamine (1:1)"[tw] OR "N-(Phosphonomethyl)glycine, compound with 2-propylamine (1:1)"[tw] OR "Isopropylamine glyphosate"[tw] OR "81591-81-3"[tw] OR "Glyphosate-trimesium"[tw] OR "Glyphosphate-trimesium"[tw] OR "Avans 330"[tw] OR "Glyphosate mono(trimethylsulfonium) salt"[tw] OR "Glyphosate trimethylsulfonium salt"[tw] OR "Glyphosate-trimesium"[tw] OR "Medallon"[tw] OR "Ouragan"[tw] OR "R 50224"[tw] OR "SC 0224"[tw] OR "Sulfosate"[tw] OR "Sulphosate"[tw] OR "Touchdown herbicide"[tw] OR "Trimethylsulfonium carboxymethylamino-methylphosphonate"[tw] OR "Trimethylsulfonium glyphosate"[tw] OR "Glycine, N-(phosphonomethyl)-, ion(1-), trimethylsulfonium"[tw] OR "Sulfosate"[tw]) NOT (("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	"Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb]) OR ("Roundup"[tw] AND (monsanto[tw] OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR "antifungal"[tw] OR "anti-fungal"[tw] OR "enzyme inhibitors"[Pharmacological Action] OR "enzyme inhibitors"[MeSH Terms] OR ("enzyme"[tw] AND inhibitor*[tw]) OR "enzyme inhibitors"[tw] OR "enzyme inhibitor"[tw] OR "herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[tw] OR "herbicide"[tw] OR "uncoupling agents"[Pharmacological Action] OR "uncoupling agents"[MeSH Terms] OR ("uncoupling"[tw] AND agent*[tw]) OR "uncoupling agent"[tw] OR "uncoupling agents"[tw] OR "pesticides"[mh] OR pesticide*[tw]))))
Toxline 2/18/2015	"Glifoglex" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "Glyphosate" OR "Glyphosphate" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phosphonomethylglycine" OR "Pondmaster" OR "Silglif" OR "yerbimat" "(Carboxymethylamino)methylphosphonic acid" OR "Carboxymethylaminomethanephosphinic acid" OR "C-K Yuyos FAV" OR "CP 67573" OR "Folusen" OR "Forsat" OR "Glialka" OR "Glifosan 747" OR "GlyGran" OR "Glyphodin A" OR "Glyphomax" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown"

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	"Lancer herbicide" OR "MON 2139" OR "MON 3539" OR "MON 6000" OR "Phorsat" OR "Phosphonomethyliminoacetic acid" OR "Rebel Garden" OR "Roundup Max" OR "Safal" OR "Scout herbicide"
	"roundup"
	34494-03-6[rn] OR 70393-85-0[rn]
	"MON 0459" OR "40465-66-5" OR "MON 14420" OR "MON 8750" OR "Roundup Hi-Load" OR "Roundup PRODry" OR "MON 8000" OR "Monsanto 8000" OR "Polado" OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate)"
	39600-42-5[rn] OR 39600-55-0[rn] OR 39600-56-1[rn] OR 39600-58-3[rn] OR 40465-59-6[rn] OR 40465-64-3[rn] OR 40465-67-6[rn] OR 40465-70-1[rn] OR 40465-90-5[rn] OR 40465-91-6[rn] OR 70901-12-1[rn] OR 114370-14-8[rn] OR 69254-40-6[rn]
	"Glyphosate potassium" OR "Glyphosate monopotassium salt" OR "Glyphosate potassium" OR "Glyphosate-potassium" OR "Monopotassium glyphosate" OR "Roundup Attack" OR "Roundup Energy" OR "Roundup Maxload" OR "Roundup Original Max" OR "Roundup Power Max" OR "Roundup Ultramax II"
	"Roundup Weathermax" OR "Touchdown Forte HiTech" OR "Transorb R" OR "Weathermax" OR "Zapp Qi" OR "Glyphosate-potassium" OR "Potassium glyphosate" OR "Potassium N-(phosphonomethyl)glycine" OR "Uragan Forte" OR "VisionMAX" OR "N-(phosphonomethyl)glycine potassium salt" OR "Glyphosate ammonium" OR "N-(phosphonomethyl)glycine ammonium salt"
	"Glyphosate-diammonium" OR "Diammonium N-(phosphonomethyl)glycine" OR "N-(phosphonomethyl)glycine diammonium salt"
	38641-94-0[rn] OR 81591-81-3[rn]
	"Glyphosate-isopropylammonium" OR "Glyphosate isopropylamine salt" OR "Azural AT" OR "CP 70139" OR "Fosulen" OR "Glifosato estrella" OR "Glycel" OR "Glycine, N-(phosphonomethyl)-, cmpd with 2-propanamine (1:1)" OR "Glyfos AU" OR "Glyfos BIO" OR "Glyphosate isopropylamine salt"
	"Glyphosate mono(isopropylamine) salt" OR "Glyphosate-isopropylammonium" OR "Glyphosate-mono(isopropylammonium)" OR "Landmaster" OR "MON 139" OR "MON 39" OR "N-(Phosphonomethyl)glycine isopropylamine salt" OR "N-(Phosphonomethyl)glycine isopropylammonium salt"
	"N-(Phosphonomethyl)glycine monoisopropylamine salt" OR "Nitosorg" OR "Utal" OR "Utal (herbicide)" OR "Vision (herbicide)" OR "2-Propanamine, compd, with N-(phosphonomethyl)glycine (1:1)" OR "Glycine, N-(phosphonomethyl)-, compd. with 2-propanamine (1:1)" OR "N-(Phosphonomethyl)glycine, compound with 2-propylamine (1:1)"
	"Isopropylamine glyphosate" OR "Glyphosate-trimesium" OR "Glyphosphate-trimesium" OR "Avans 330" OR "Glyphosate mono(trimethylsulfonium) salt" OR "Glyphosate trimethylsulfonium salt" OR "Glyphosate-trimesium" OR "Medallon" OR "Ouragan" OR "R 50224" OR "SC 0224" OR "Sulfosate"
	"Sulphosate" OR "Touchdown herbicide" OR "Trimethylsulfonium carboxymethylamino-methylphosphonate" OR "Trimethylsulfonium glyphosate" OR "Glycine, N- N-phosphonemethyl)-, ion(1-), trimethylsulfonium"
Toxcenter 2/2017	FILE 'TOXCENTER' ENTERED AT 19:21:56 ON 18 FEB 2015 CHARGED TO COST=EH011.05.01.01 L1 8342 SEA 1071-83-6 L2 63 SEA 34494-03-6 OR 40465-66-5 OR 70393-85-0 L3 8 SEA L2 NOT L1 L4 53 SEA 39600-42-5 OR 39600-55-0 OR 39600-56-1 OR 39600-58-3 OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	40465-59-6 OR 40465-64-3 OR 40465-67-6 OR 40465-70-1 OR 40465-90-5 OR 40465-91-6
	L5 59 SEA 70901-12-1 OR 114370-14-8 OR 69254-40-6
	L6 1828 SEA 38641-94-0 OR 81591-81-3
	L7 8369 SEA L1 OR L2 OR L4 OR L5
	L8 5041 SEA L7 NOT (PATENT/DT OR TSCATS/FS)
	ACT TOXQUERY/Q

	L9 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L10 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L11 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L12 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L13 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L14 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L15 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L16 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L17 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L18 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L19 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L20 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L21 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L22 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L23 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L24 QUE (ENDOCRIN? AND DISRUPT?)
	L25 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L26 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L27 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L28 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L29 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L30 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	L31 QUE (NEPHROTOX? OR HEPATOTOX?)
	L32 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L33 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L34 QUE L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33
	L35 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L36 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L37 QUE L34 OR L35 OR L36
	L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L39 QUE L37 OR L38

	L40 2675 SEA L8 AND L37
	L41 525 SEA L40 AND MEDLINE/FS
	L42 833 SEA L40 AND BIOSIS/FS
	L43 1263 SEA L40 AND CAPLUS/FS
	L44 0 SEA L40 AND IPA/FS
	L45 54 SEA L40 NOT (L41 OR L42 OR L43)
	L46 2064 DUP REM L41 L42 L43 L45 (611 DUPLICATES REMOVED)
	ANSWERS '1-2064' FROM FILE TOXCENTER
	L*** DEL 525 S L40 AND MEDLINE/FS
	L*** DEL 525 S L40 AND MEDLINE/FS
	L47 525 SEA L46
	L*** DEL 833 S L40 AND BIOSIS/FS
	L*** DEL 833 S L40 AND BIOSIS/FS
	L48 644 SEA L46
	L*** DEL 1263 S L40 AND CAPLUS/FS
	L*** DEL 1263 S L40 AND CAPLUS/FS
	L49 859 SEA L46
	L*** DEL 54 S L40 NOT (L41 OR L42 OR L43)
	L*** DEL 54 S L40 NOT (L41 OR L42 OR L43)
	L50 36 SEA L46
	L51 1539 SEA (L47 OR L48 OR L49 OR L50) NOT MEDLINE/FS
	L52 1532 SEA L51 AND L1
	L53 7 SEA L51 NOT L52
	D SCAN L53
	L54 688 SEA L6 NOT L7
	L55 485 SEA L54 NOT (PATENT/DT OR TSCATS/FS)
	L56 314 SEA L55 AND L37
	L57 0 SEA L56 AND MEDLINE/FS
	L58 85 SEA L56 AND BIOSIS/FS
	L59 218 SEA L56 AND CAPLUS/FS

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	L60 1 SEA L56 AND IPA/FS L61 274 DUP REM L56 (40 DUPLICATES REMOVED) ANSWERS '1-274' FROM FILE TOXCENTER D SCAN L52

1

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
2/2015	Compounds searched: 1071-83-6; 34494-03-6; 40465-66-5; 70393-85-0; 38641-94-0; 81591-81-3
NTP	
2/2015	"1071-83-6" OR "Glifoglex" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "Glyphosate" OR "Glyphosphate" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phosphonomethylglycine" OR "Pondmaster" OR "Silglif" OR "yerbimat" "34494-03-6" OR "40465-66-5" OR "70393-85-0" OR "MON 0459" OR "MON 14420" OR "MON 8750" OR "Roundup Hi-Load" OR "Roundup PRODry" OR "MON 8000" OR "Monsanto 8000" OR "Polado" OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate)" "38641-94-0" OR "Glyphosate-isopropylammonium" OR "Glyphosate isopropylamine salt" OR "Azural AT" OR "Buggy" OR "CP 70139" OR "Fosulen" OR "Glifosato estrella" OR "Glycel" OR "Glyfos AU" OR "Glyfos BIO" OR "Glyphosate isopropylamine salt" OR "Glyphosate mono(isopropylamine) salt" OR "Glyphosate-isopropylammonium" OR "Glyphosate-mono(isopropylammonium)" OR "Landmaster" OR "MON 139" OR "MON 39" OR "N-(Phosphonomethyl)glycine isopropylamine salt" OR "N-(Phosphonomethyl)glycine isopropylammonium salt" OR "N-(Phosphonomethyl)glycine monoisopropylamine salt" OR "Nitosorg" OR "Ron-do" OR "Utal" OR "Vision (herbicide)" OR "Roundup" OR "Isopropylamine glyphosate" OR "81591-81-3" OR "Glyphosate-trimesium" OR "Glyphosphate-trimesium" OR "Avans 330" OR "Glyphosate mono(trimethylsulfonium) salt" OR "Glyphosate trimethylsulfonium salt" OR "Glyphosate-trimesium" OR "Medallon" OR "Ouragan" OR "R 50224" OR "SC 0224" OR "Sulfosate" OR "Sulphosate" OR "Touchdown" OR "Trimethylsulfonium carboxymethylamino-methylphosphonate" OR "Trimethylsulfonium glyphosate"
NPIRS 2/2015	PC Codes searched: 417300; 103603; 103613; 103604; 103607; 103601; 128501
NIH RePORTER	
4/2017	Text Search: "Carboxymethylamino)methylphosphonic acid" OR "2-Propanamine, compd, with N-(phosphonomethyl)glycine (1:1)" OR "Avans 330" OR "Azural AT" OR "C-K Yuyos FAV" OR "Carboxymethylaminomethanephosphinic acid" OR "CP 67573" OR "CP 70139" OR "Diammonium N-(phosphonomethyl)glycine" OR "Folusen" OR "Forsat" OR "Fosulen" OR "Glialka" OR "Glifoglex" OR "Glifosan 747" OR "Glifosato estrella" OR "gliphosate" OR "Gliz" OR "Glycel" OR "Glycine, N-(phosphonomethyl)-, cmpd with 2-propanamine (1:1)" OR "Glycine, N-(phosphonomethyl)-, compd. with 2-propanamine (1:1)" OR "Glycine, N-(phosphonomethyl)-, ion(1-), trimethylsulfonium" OR "Glyfos" OR "Glyfos AU" OR "Glyfos BIO" OR "GlyGran" OR "Glyphodin A" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Glyphomax" OR "Glyphosate" OR "Glyphosphate" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown" OR "Lancer herbicide" OR "Landmaster" OR "Medallon" OR "MON 0459" OR "MON 139" OR "MON 14420" OR "MON 2139" OR "MON 3539" OR "MON 39" OR "MON 6000" OR "MON 8000" OR "MON 8750" OR "Monsanto 8000" OR "N-(phosphonomethyl)-Glycine" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)glycine ammonium salt" OR "N-(phosphonomethyl)glycine diammonium salt" OR "N-(Phosphonomethyl)glycine isopropylamine salt" OR "N-(Phosphonomethyl)glycine isopropylammonium salt" OR "N-(Phosphonomethyl)glycine monoisopropylamine salt" OR "N-(phosphonomethyl)glycine potassium salt" OR "N-(Phosphonomethyl)glycine, compound with 2-propylamine (1:1)" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Nitosorg" OR "Ouragan" OR "Phorsat" OR "Phosphonomethylglycine" OR "Phosphonomethyliminoacetic acid" OR "Polado" OR "Pondmaster" OR "Potassium N-(phosphonomethyl)glycine" OR "R 50224" OR "Rebel Garden" OR "Ron-do" OR "Roundup" OR "Safal" OR "SC 0224" OR "Scout herbicide" OR "Silglif" OR "Sulfosate" OR "Sulphosate" OR "Touchdown Forte HiTech" OR "Touchdown herbicide" OR "Transorb R" OR "Trimethylsulfonium carboxymethylamino-methylphosphonate" OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate" OR "Uragan Forte" OR "Utal" OR "Vision herbicide" OR "VisionMAX" OR "Weathermax" OR "yerbimat" OR "Zapp Qi" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects, 2017, 2016, 2015, 2014, 2013, 2012
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2015 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 5,506
- Number of records identified from other strategies: 173
- Total number of records to undergo literature screening: 5,679

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on glyphosate:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

- Number of titles and abstracts screened: 5,679

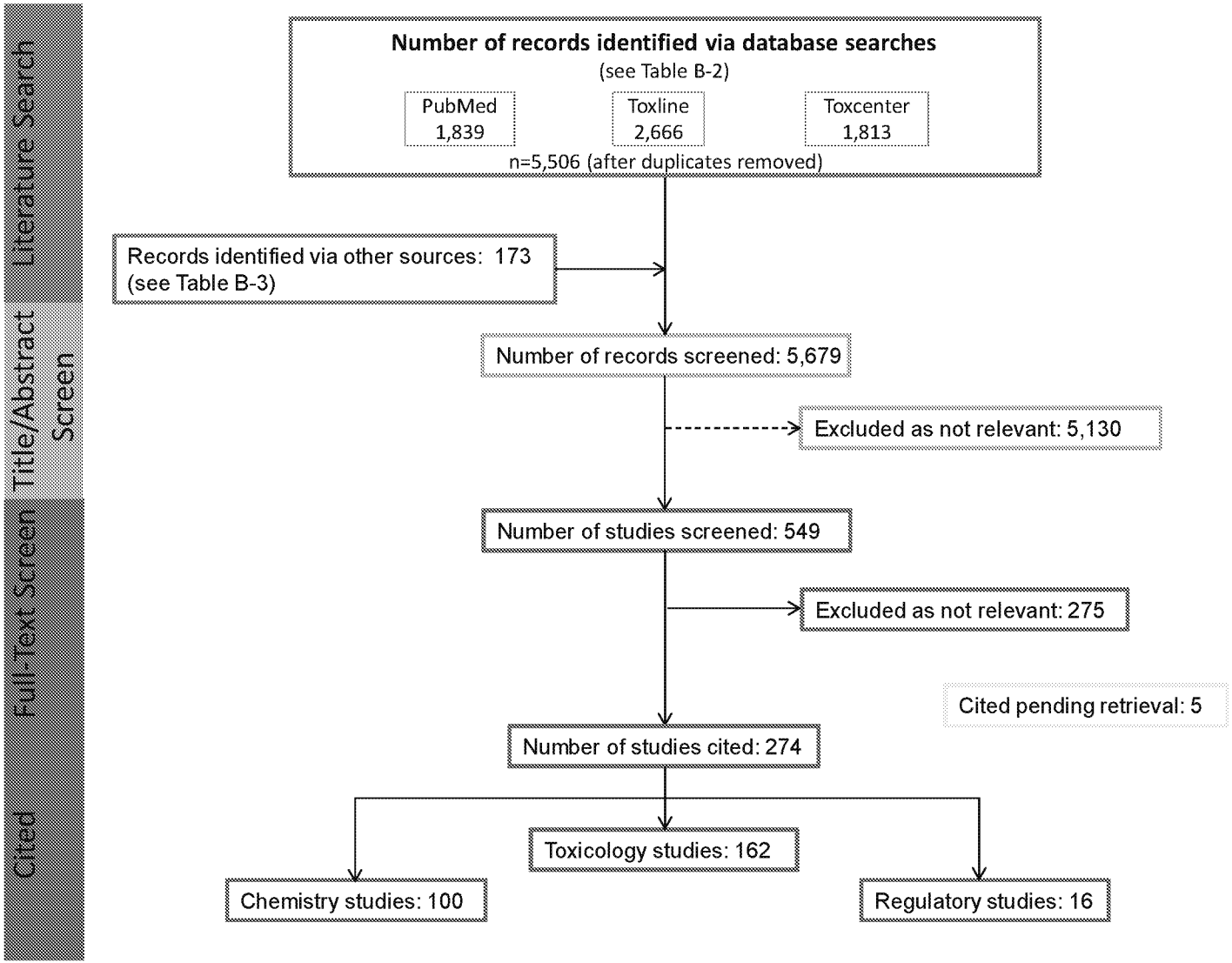
- Number of studies considered relevant and moved to the next step: 549

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 549
- Total number of studies cited in the profile: 274

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. February 2015 Literature Search Results and Screen for Glyphosate



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to "Chemical X" via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX C

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[b]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	**Lifetime** (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

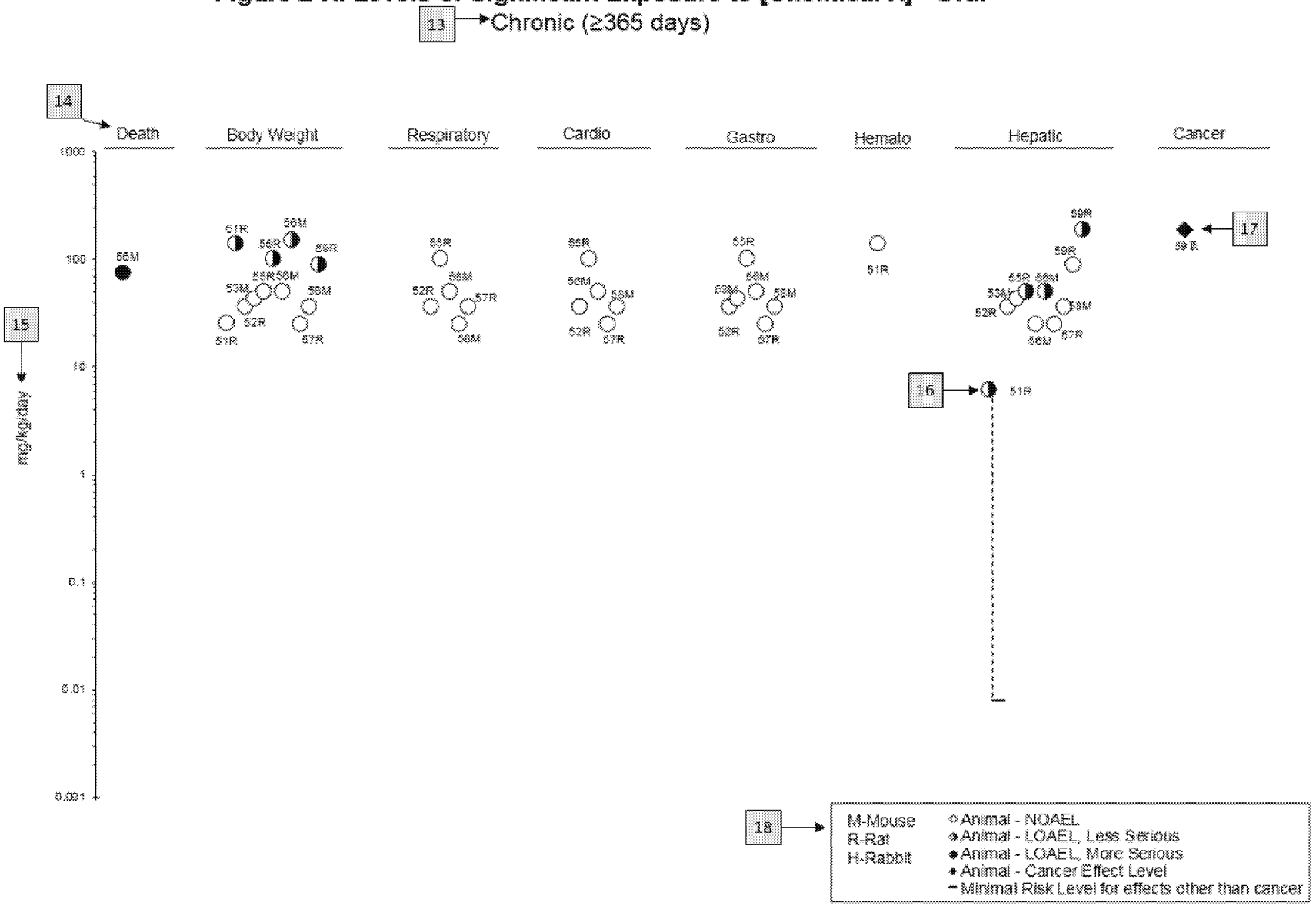
(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

1

APPENDIX C

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



1

APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) $\geq$1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

1	FR	Federal Register
2	FSH	follicle stimulating hormone
3	g	gram
4	GC	gas chromatography
5	gd	gestational day
6	GGT	γ-glutamyl transferase
7	GRAS	generally recognized as safe
8	HEC	human equivalent concentration
9	HED	human equivalent dose
10	HHS	Department of Health and Human Services
11	HPLC	high-performance liquid chromatography
12	HSDB	Hazardous Substance Data Bank
13	IARC	International Agency for Research on Cancer
14	IDLH	immediately dangerous to life and health
15	IRIS	Integrated Risk Information System
16	Kd	adsorption ratio
17	kg	kilogram
18	kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
19	K_{oc}	organic carbon partition coefficient
20	K_{ow}	octanol-water partition coefficient
21	L	liter
22	LC	liquid chromatography
23	LC_{50}	lethal concentration, 50% kill
24	LC_{Lo}	lethal concentration, low
25	LD_{50}	lethal dose, 50% kill
26	LD_{Lo}	lethal dose, low
27	LDH	lactic dehydrogenase
28	LH	luteinizing hormone
29	LOAEL	lowest-observed-adverse-effect level
30	LSE	Level of Significant Exposure
31	LT_{50}	lethal time, 50% kill
32	m	meter
33	mCi	millicurie
34	MCL	maximum contaminant level
35	MCLG	maximum contaminant level goal
36	MF	modifying factor
37	mg	milligram
38	mL	milliliter
39	mm	millimeter
40	mmHg	millimeters of mercury
41	mmol	millimole
42	MRL	Minimal Risk Level
43	MS	mass spectrometry
44	MSHA	Mine Safety and Health Administration
45	Mt	metric ton
46	NAAQS	National Ambient Air Quality Standard
47	NAS	National Academy of Science
48	NCEH	National Center for Environmental Health
49	ND	not detected
50	ng	nanogram
51	NHANES	National Health and Nutrition Examination Survey

NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PEHSU	Pediatric Environmental Health Specialty Unit
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

1	USNRC	U.S. Nuclear Regulatory Commission
2	VOC	volatile organic compound
3	WBC	white blood cell
4	WHO	World Health Organization
5		
6	>	greater than
7	≥	greater than or equal to
8	=	equal to
9	<	less than
10	≤	less than or equal to
11	%	percent
12	α	alpha
13	β	beta
14	γ	gamma
15	δ	delta
16	μm	micrometer
17	μg	microgram
18	q_1^*	cancer slope factor
19	–	negative
20	+	positive
21	(+)	weakly positive result
22	(–)	weakly negative result